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Review

LUPUS NEPHROPATHY. ANATOMOCLINICAL EXPERIENCE

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Abstract

Lupus nephropathy (LN) is one of the most severe systemic lupus erythematosus manifestations, representing a major cause of morbidity and mortality. Its incidence is variable, depending on the methods used in the diagnosis.

Based on clinical-biological picture, LN incidence is between 60-80%, whereas based on histology, the incidence is between 95-100%. In LN are affected all renal structures: glomeruli (the most important involvement), tubules, interstitium and vessels. The clinical-biological picture is variable: nephritic syndrome, nephrotic syndrome, renal insufficiency syndrome, hypertensive syndrome, isolated urinary manifestations, tubular insufficiency syndrome, isolated interstitial syndrome, pseudopyelonephritis.

It isn´t a strict correlation between clinical-biological and histological pictures. Histological diagnosis, performed with renal biopsy and examination of renal tissue fragment in light microscopy, immunofluorescence, electron microscopy, is necessary. Histological study will answer to many questions: Has patient lupus nephropathy or another renal pathology associated or independent from lupus disease? What are the affected renal structures? What is the grade of renal lesions activity or chronicity?

*ISN/RPS **classification** of LN (2003) identified six classes of LN: minimal mesangial LN (class I), mesangial proliferative NL (class II), focal LN (Class III), diffuse LN (class IV), membranous LN (class V), advanced sclerosis LN (class VI). Tubulo-interstitial (inflammatory infiltrate, interstitial fibrosis, tubular atrophy) and vascular (vasculopathy, vasculitis, thrombotic microangiopathy, sclerosis) lesions are presented. Renal lesions may be active or chronic.*

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Before renal biopsy, it will be assessed the risks of this method versus the risks which result from the incomplete or missed diagnosis, favoring the progression of a potential treatable renal disease or using drugs with important sides effects. Based on the histological study results, it will be established the renal prognosis and it will be choose an adequate immunosuppressive therapy.

Keywords: *lupus nephropathy, renal histopathologic study, immunosuppressive therapy*

Rezumat

Nefropatia lupică (LN) este una din cele mai severe manifestări sistemice ale lupusului eritematos, reprezentând o cauză majoră de morbiditate şi de mortalitate. Incidența este variabilă, in funcție de metoda utilizată în diagnostic.

Raportat la aspectul clinico-biologic, incidența este de 60-80%, iar anamnestic, de 95-100%. În LN sunt afectate toate structurile renale: glomeruli (cea mai importantă afectare), tubuli, interstiţiu şi vase.

Aspectul clinico-biologic este variabil: sindrom nefritic sau nefrotic, insuficiență renală, sindrom hipertensiv sau manifestări urinare izolate, sindrom de insuficiență tubulară, sindrom interstiţial izolat sau pseudopielonefrită.

Nu există o corelație strictă intre aspectul clinico-biologic şi cel histopatologic. Diagnosticul histopatologic se realizează pe baza examinării microscopice, a fragmentelor tisulare renale recoltate prin biopsie şi prin imunofluoreşcență şi microscopie electronică. Studiul histopatologic ridică câteva probleme: pacientul are nefropatie lupică sau altă patologie renală independentă de lupus? În ce măsură sunt afectate structurile renale şi care este gradul lor de activitate sau de cronicizare?

***Clasificarea** ISN/RPS a LN din 2003, identifică 6 categorii: clasa I: minimă LN mezangială, II: mezangială proliferativă, III: LN focală, IV: difuză, V: LN membranoasă, VI: scleroză avansată. Există leziuni tubulo-interstiţiale: infiltrat inflamator, fibroză interstiţială, atrofie tubulară şi vasculare: vasculopatie, vasculite, microangiopatie trombotică, scleroză. Leziunile renale pot fi active sau cronice.*

Trebuie evaluat riscul biopsiei renale şi riscul unui eventual diagnostic incomplet, ce ar favoriza progresia unei boli renale tratabile sau folosirea unor medicamente cu importante efecte secundare.

Pe baza examenului histopatologic, se evaluează prognosticul şi se stabileşte o terapie imunosupresoare adecvată

Cuvinte-cheie: *nefropatie lupică, examen histopatologic renal, terapie imnosupresoare*

Systemic lupus erythematosus (SLE) is a disorder with unknown etiology and with autoimmune pathogenesis, characterized by chronic inflammatory process associated with the production of antinuclear, cytoplasmic or membrane antigen (Ag) antibody (Ab). SLE is the prototypical autoimmune disease (1).

The clinical aspect is extremely diverse, actually reflecting the chronic inflammation of various organs and systems. The skin, joints and kidneys seem to be most commonly affected in lupus, however, practically any organ or system may present morphofunctional alterations secondary to SLE. Immune disorders include the presence of antibodies (the most common being antinuclear, anti-double stranded DNA (dsDNA antibodies), hypergammaglobulinemia, hypocomplementemia. The histological study of the affected organs shows the presence of immune complexes and complement factors at this level (2).

Diagnosis is based on the SLE diagnostic criteria **(table 1)**; positive diagnosis is confirmed by the presence of at least four criteria (3). The presence of less than four criteria defines latent or incomplete lupus (1).

Table no 1: Classification of SLE

Criterion	Definition
Malar rash	- fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
Discoid rash	- erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
Photosensitivity	- skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
Oral ulcers	- oral or nasopharyngeal ulceration, usually painless, observed by the physician
Arthritis	- nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
Serositis	- pleuritis: history of pleuritic pain or rub heard by the physician or evidence of pleural effusion or - pericarditis: documented by ECG, rub, or evidence of pericardial effusion
Renal disorder	- persistent proteinuria greater than 0.5 g/24 hours or greater than 3+ if quantitation not performed or - cellular casts: red cell, granular, mixed
Neurologic disorder	- seizures, in the absence of drugs or known metabolic disorders (uremia, ketoacidosis, or electrolyte imbalance) or - psychosis, in the absence of drugs or known metabolic disorders (uremia, ketoacidosis, or electrolyte imbalance)

Hematologic disorder	- hemolytic anemia, with reticulocytosis or - leukopenia (less than 4000/mm^3) on two or more occasions or - lymphopenia (less than 1500/mm^3) on two or more occasions or - thrombocytopenia (less than 100000/mm^3) in the absence of offending drugs
Immunologic disorder	- antibody to native DNA in abnormal titer or - antibody to Sm nuclear antigen or - antiphospholipid antibodies identified by: an abnormal serum level of IgG or IgM anticardiopin antibodies, a positive test result for lupus anticoagulant using a standard method, or a false-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test
Antinuclear antibody	- an abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome

Lupus nephropathy (LN) is one of the most severe manifestations of SLE, being a major cause of morbidity and mortality. Renal involvement plays a decisive role in the development of the disease, kidney failure being one of the main causes of mortality in SLE (4, 5).

The school of internal medicine and nephrology of Timişoara has been closely involved in the study of major collagenosis, both from a clinicobiological and histological point of view. Thus, the first research in lupus-induced renal disorders was initiated in the '60s by Professor C. Zosin and Associate Professor. N. Mănescu (6, 7, 8, 9, 10, 11).

First research was continued by Professor I. Romoşan in the '90^s (12, 13), and later on by his collaborators (14, 15, 16, 17).

The incidence of LN varies according to the diagnostic methods used. If diagnosis is defined solely based on clinicobiological criteria (proteinuria, hematuria, cylindruria, nitrogen retention, high blood pressure, edematous syndrome), then the incidence of LN ranges between 60 and 80 per cent. However, diagnosis defined on the basis of the histological exam of the specimen obtained by percutaneous renal biopsy shows an incidence ranging between 95-100 per cent (18, 19, 20).

Kidney involvement in SLE is the consequence of renal morphofunctional characteristics: high blood flow, extensive filtration surface, high hydrostatic

forces, the presence of C_{3b} and F_c in the endothelium and mesangium, the electrical charge of glomerular capillary walls. The type and severity of the renal damage depends on the characteristics, quantity and location of immune complexes (15, 21).

LN may affect all renal structures: glomeruli (the most significant involvement) (**figures no. 1, 2**), tubules (**figure no. 3**), interstitium, as well as vessels.

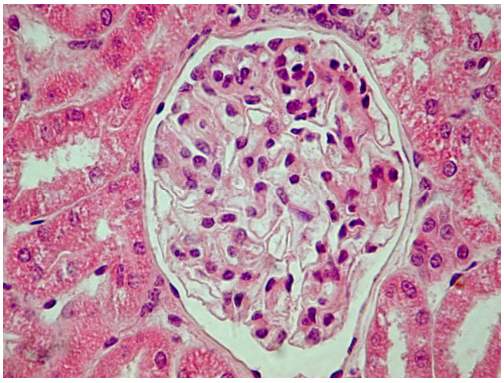

Figure 1. Hypercellular renal corpuscle, with abnormal accumulation of mesangial matrix. Note focal wire loop capillaries. HE x400

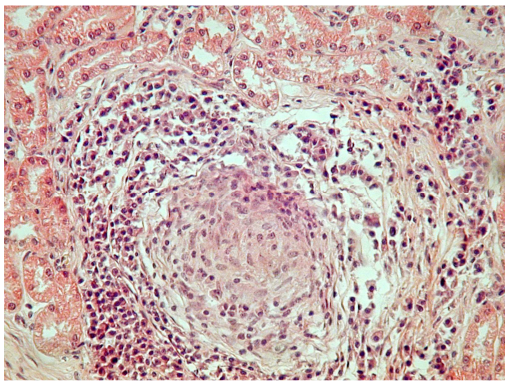

Figure 2. Fibrous change of the renal corpuscle and abundant inflammatory cells in advanced-stage lupus nephritis. HE x200.

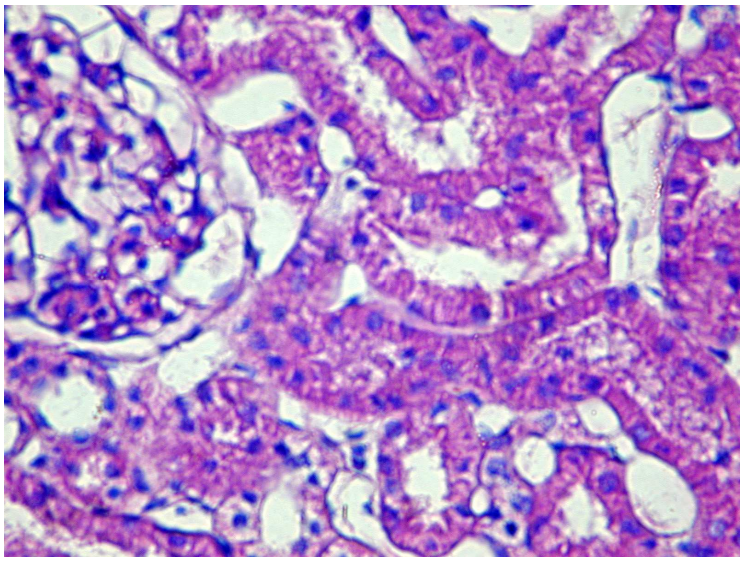

Figure 3. Disorganization of the tubular system, dilation and focal necrosis. PAS reaction x400

Although glomerular involvement plays an essential role in prognosis, some patients had severe tubulointerstitial or vascular damage despite only slight glomerular damage (22). At the same time, lupus may be associated with various disorders which also involve the kidney. Associated antiphospholipid syndrome induces thrombotic microangiopathy in the kidney, and the use of NSAIDs leads to the development of drug-induced nephropathy (16, 23, 24).

Clinico-biological manifestations of LN are extremely varied. Renal involvement may be present upon SLE diagnosis in 25 per cent of the patients; more than 60 per cent of the patients diagnosed with SLE will develop clinically manifest renal disorders during the course of the disease. In 5 per cent of the cases, urinary alterations may already develop years before the occurrence of SLE diagnostic criteria. Special attention needs to be paid to patients with incomplete SLE, where the development of proteinuria confirms the diagnosis. That is why this group of patients requires a thorough and repeated investigation of the renal function (5, 25).

From a clinico-biological point of view, SLE may occur under various manifestations **(table 2).**

Table no. 2: The clinicobiological picture of LN

Clinicobiological picture	Characteristics
Nephritic syndrome	- associates telescope urinary sediment (Krupp)
Nephrotic syndrome	- impure, progresses with gammaglobulin increase
Renal failure syndrome	- acute - rapidly progressive - chronic (the endstage of LN progression)
Hypertensive syndrome	- associated with other clinicobiological syndromes
Asymptomatic urinary anomalies	- isolated proteinuria - isolated haematuria
Tubular failure syndrome	- associated with other clinical syndromes - manifested as: urine concentration deficit or distal renal tubular acidosis
Isolated interstitial syndrome	- occurs rarely - manifests as: tubular proteinuria, microscopic haematuria, leucocyturia
Pseudopyelonephritic	- sterile leucocyturia, negative K.B. - minimal, tubular proteinuria

Proteinuria is present in almost every patient, with variable intensity, up to nephrotic syndrome. Electrophoretic pattern shows unselective or mixed proteinuria, rarely just tubular, depending on the predominantly involved histological structures. Another urinary sign is microscopic haematuria, which in

very few cases may even be macroscopic. High blood pressure is associated with severe LN, while oedema point to the presence of nephrotic syndrome. Nycturia characterizes tubulointerstitial involvement. Azotemia confirms the existence of kidney failure. In some cases, the onset of LN may arise as acute kidney failure, commonly associated with other severe manifestations (myocarditis, involvement of the central nervous system) (3, 5, 26).

This clinico-biological picture is also common to other renal disorders that can be addressed by specific therapy.

The antiphospholipid syndrome associated to SLE (15 per cent of the patients develop antiphospholipid antibodies) induces renal thrombotic microangiopathy, which has the following clinicobiological picture: proteinuria, haematuria, azotemia. Thrombotic microangiopathy can be addressed with specific therapy; consequently, the presence of this histological damage has to be corroborated or disproved, mainly for patients with existing antiphospholipid Ab (24). The use of NSAIDs in the treatment of extrarenal SLE manifestations may generate acute or chronic tubulointerstitial nephropathy (proteinuria, leucocyturia, haematuria, cylindruria, azotemia), or minimal-change glomerulopathy (nephrotic syndrome) (16). Last, but not least, primitive glomerular nephropathy associated with lupus should be excluded.

This clinicobiological variability is the expression of the diverse histological picture, which makes histological diagnosis of LN mandatory (27).

Histological exploration should address several questions:

- Does the patient have LN or another renal pathology, either independent or associated with lupus ?
- Which is the predominantly involved renal structure ?
- What is the degree of activity or chronicity of the existing renal damage ?

The answers to these questions will outline an effective therapeutic scheme which will focus on two aspects: on the one hand, it will preserve/improve renal function, on the other hand, it will not expose the patient to the secondary effects inherent to cytotoxic therapy.

Histological study offers information about the predominantly damaged renal structure in LN (glomeruli, tubules, interstitium, vessels). For the results to be interpretable, the specimen obtained by percutaneous renal biopsy should contain at least ten glomeruli (28). Immunofluorescence (IF) requires the use of anti-IgG, -IgA, -IgM serums, light k and λ chains, complement components (C3, C1q) (29). Electron microscopy (EM) is reserved for the cases where histopathological diagnosis can not be established by light microscopy (LM) and IF (30). Renal histological damage together with the renal function upon LN diagnosis represent the prognostic factors which determine the therapeutic attitude (5).

There is no precise correlation between the clinico-biological manifestations and the histological type in LN. Several studies have shown that a diagnosis based solely on clinicobiological data is inaccurate. Even patients without a clinically manifest kidney disorder may often have mesangial immune deposits, therefore the clinico-biological picture has no predictive value for the severity of

histological damage (31, 32, 33). Normally, proteinuria < 1 g/24 hours appears in mesangial lupus nephropathy and tubulointerstitial nephropathy; proteinuria between 1-3 g/24 hs is common in: focal or diffuse proliferative glomerulonephritis, as well as in membranous one; proteinuria> 3.5 g/24 hours is characteristic for diffuse or membranous glomerulonephritis. There have also been cases of nephrotic proteinuria, when the histological study showed the fusion of podocyte processes, associated or not with endocapillary alterations.

Haematuria may be present in: mesangial, focal proliferative or diffuse lupus glomerulonephritic, and in tubulointerstitial nephropathy. Cylindruria is associated with major proteinuria and haematuria, while high blood pressure is present in certain forms of focal proliferative glomerulonephritis, in diffuse proliferative glomerulonephritis and, in later stages, in membranous glomerulonephritis and tubulointerstitial nephropathy.

Studying a group of patients with LN, with proteinuria < 1 g/24 hours and normal renal function, Christopher-Stine I. and collab. have identified type II, III, IV, and even V of lupus glomerular nephropathy. What's more, in a case of focal lupus glomerulonephritis, proteinuria was < 500 mg/24 hours and haematuria was absent (27, 29, 34, 35, 36, 37).

Mănescu, Romoşan and collab. have demonstrated the weak correlation between the clinicobiological manifestation and the histological type in LN (11, 12, 13). Several associations have been proposed between the various histological types of LN, the activity of the disease and the presence of serum markers (anti-native DNA antibodies, anti-Sm, anti-C_{1q}). Although anti-native DNA antibodies are correlated with the activity of the disease and with the histological type, this correlation is not strong enough to intensify the therapeutic attitude whenever there is an increase in these antibodies. Apparently, anti-C_{1q} antibodies might be used in estimating relapse risk in NL (3, 38).

The first WHO classification of lupus nephropathy belonged to Pirani and Pollak in 1973 (**table 3**).

Table no 3. World Health Organization (WHO) classification of lupus nephritis (1974)

Class I	Normal glomeruli (by light microscopy, immunofluorescence, and electron microscopy)
Class II	Purely mesangial disease a) normocellular mesangium by light microscopy, but mesangial deposits by immunofluorescence or electronic microscopy b) mesangial hypercellularity with mesangial deposits by immunofluorescence or electron microscopy
Class III	Focal proliferative glomerulonephritis (< 50%)
Class IV	Diffuse proliferative glomerulonephritis (≥ 50%)
Class V	Membranous glomerulonephritis

This classification only addresses the glomerular compartment, disregarding the tubulointerstitial and vascular ones. Subsequently, the WHO proposed a new NL classification system (**table 4**) (29).

Table no. 4: World Health Organization (WHO) morphologic classification of lupus nephritis (1982)

Class I	Normal glomeruli a) by all techniques b) normal by light microscopy, but deposits by immunofluorescence, and electron microscopy)
Class II	Pure mesangial alterations (mesangiopathy) a) mesangial widening and/or mild hypercellularity (+) b) moderate mesangial hypercellularity (++)
Class III	Focal segmental glomerulonephritis (associated with mild or moderate mesangial alterations) a) with "active" necrotizing lesions b) with "active" and sclerosing lesions c) with sclerosing lesions
Class IV	Diffuse proliferative glomerulonephritis (severe mesangial, endocapillary or mesangiocapillary proliferation and/or extensive subendothelial deposits) a) without segmental lesions b) with "active" necrotizing lesions c) with "active" and sclerosing lesions d) with sclerosing lesions
Class V	Diffuse membranous glomerulonephritis a) pure membranous glomerulonephritis b) associated with lesions of class II c) associated with lesions of class III d) associated with lesions of class IV
Class VI	Advanced sclerosing glomerulonephritis

In 2003, the International Society of Nephrology/The Renal Pathology Society (ISN/RSP) propose a new LN classification system (**table no. 5**) (19, 39, 40).

Table no *5* International Society of Nephrology/Renal Pathology Society (ISN/RSP) classification of lupus nephritis (2003)

Class I	***Minimal mesangial lupus nephritis:*** normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence
Class II	***Mesangial proliferative lupus nephritis:*** - purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposits;

	- may be a few isolated subepithelial or subendothelial deposits visible by immunofluorescence or electron microscopy, but not by light microscopy
Class III	***Focal lupus nephritis:*** active or inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving < 50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations;
Class III (A)	active lesions: focal proliferative lupus nephritis
Class III (A/C)	active and chronic lesions: focal proliferative and sclerosing lupus nephritis
Class III (C)	chronic inactive lesions with glomerular scars: focal sclerosing lupus nephritis
Class IV	***Diffuse lupus nephritis:*** active or inactive diffuse, segmental or global endo- or extracapillary glomerulonephritis involving ≥ 50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations; this class is divided into diffuse segmental (IV-S) lupus nephritis when ≥ 50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G) lupus nephritis when ≥ 50% of the involved glomeruli have global lesions;
Class IV-S (A)	active lesions: diffuse segmental proliferative lupus nephritis
Class IV-G (A)	active lesions: diffuse global proliferative lupus nephritis
Class IV-S (A/C)	active and chronic lesions: diffuse segmental proliferative and sclerosing lupus nephritis
Class IV-G (A/C)	active and chronic lesions: diffuse global proliferative and sclerosing lupus nephritis
Class IV-S (C)	chronic inactive lesions with glomerular scars: diffuse segmental sclerosing lupus nephritis
Class IV-G (C)	chronic inactive lesions with glomerular scars: diffuse global sclerosing lupus nephritis
Class V	***Membranous lupus nephritis:*** - global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy, immunofluorescence or electron microscopy, with or without mesangial alterations; - class V lupus nephritis may occur in combination with class III or IV in which case both will be diagnosed; - class V lupus nephritis show advanced sclerosis
Class VI	***Advanced sclerosis lupus nephritis:*** ≥ 90% of glomeruli globally sclerosed without residual activity

Unlike the initial classification (1974), the absence of any glomerular anomalies in LM, IF, EM is no longer compatible with class I. The presence of any subendothelial deposit or glomerular scar is incompatible with class II, placing the respective damage in class III or IV, according to the extension and distribution of the deposits, or glomerular scars respectively.

In class III (focal LN), the impaired glomeruli usually have segmental endocapillary proliferative damage or glomerular scars with/without capillary wall necrosis and epithelial crescents. The deposits are mostly subendothelial, usually with a segmental distribution. There are glomeruli with both active and inactive, sclerotic damage. Mesangial alterations (mesangial proliferation or immune deposits at this level) may accompany the focal damage. Tubulointerstitial or vascular damage may be associated with glomerular damage. The combination of class III with class V requires the presence of membranous lesions in at least 50 per cent of the glomerular population (discernible in LM, IF, EM) (29, 39).

Class IV (diffuse LN) is subdivided into: IV-S (segmental diffuse LN), when over 50 per cent of the impaired glomeruli have segmental damage, and IV-G (global diffuse LN), when over 50 per cent of the impaired glomeruli have global damage. IV-S class is usually characterized by segmental endocapillary proliferation, with/without necrosis. IV-G class is characterized by diffuse and global, endocapillary, extracapillary or mesangiocapillary proliferation, or extensive "wire-loop" lesion. Any type of active damage may be present. Seldom one can find diffuse and global subendothelial glomerular deposits, with/without minimal cell proliferation. Tubulointerstitial and vascular damage is much more severe. The combination of class IV and V is characterized by the presence of membranous damage in at least 50 per cent of the glomeruli (discernible in LM, IF, EM) (29, 41).

Membranous lupus nephropathy (class V) may be associated with a certain degree of mesangial proliferation (42).

Lupus nephropathy with advanced sclerosis is the consequence of the progression of class III, IV or V in time. At this stage, the elements signaling the activity of the disease might be missing. Without previous renal biopsy, it is impossible to determine the class of LN that developed into advanced glomerular sclerosis (29, 43).

Glomerular immune deposits characteristics for LN, and detected in IF, contain polyclonal IgG and C_3 (always), C_{1q} (in most cases), and IgA, IgM (variably). Glomerular deposits consisting exclusively of IgA and/or IgM exclude the LN diagnosis (29, 39, 40).

The tubulointerstitial level contains: inflammatory infiltration (T CD45RO lymphocytes, B CD45RA lymphocytes, CD68 macrophages), tubular atrophy, interstitial fibrosis. Immunofluorescence shows deposits of IgG, C_3, C_{1q} along the tubular basement membrane and in the interstitium, while EM shows electron-dense deposits in the same location. Acute interstitial alterations and tubulointerstitial immune deposits are common in class III and class IV lupus glomerulonephritis. Interstitial fibrosis and tubular atrophy represent chronic damage, and there is a reverse correlation between the degree of chronic tubulointerstitial damage and renal prognosis (5, 37).

Vascular renal damage in LN is a poor prognostic marker. Vascular damage in LN was first described by Klemperer in 1941 (44). There are four types of vascular alterations in SLE: lupus vasculopathy, thrombotic microangiopathy (associated with the antiphospholipid syndrome), lupus vasculitis, renal vessel arterio-/arteriolosclerosis. Lupus vasculopathy, common in class IV LN, predominantly affects preglomerular arterioles, as well as interlobar arteries. At this level, we can find luminal and intimal eosinophil deposits, with endothelial thickening and media muscle cell degeneration, with absent inflammatory infiltration. Immunofluorescence shows immunoglobulin and complement deposits. Lupus vasculitis, seldom identified, is characterized by fibrinoid necrosis associated with cellular inflammatory infiltration of the arterial wall, with poor renal prognosis, requiring intensified immunosuppressive therapy. The fibrous thickeninig of the vascular intima, without necrosis, proliferation or thrombus formation, defines arterio-, respectively arteriolosclerosis (5, 45).

Besides defining the histological diagnosis and the classification of LN, renal biopsy provides information about the activity/chronicity of existing renal lesions (**table 6**), playing an important role in prognosis (46). Active damage is potentially reversible, requiring and intensified therapy, while chronic damage is irreversible but important for renal prognosis. Some authors consider that activity index (AI) > 12, and mainly chronicity index (CI) > 4, indicate poor renal prognosis (5).

Table no. 6: Classification of renal lesions in lupus nephropathy

Lesions	
Active	**Chronic**
Glomerular: - endocapillary proliferation - fibrinoid necrosis and karyorrhexis - cellular crescents - wire loop deposits - leukocyte infiltration *Tubulointerstitial*: - interstitial inflammation	*Glomerular*: - glomerulosclerosis - fibrous crescents *Tubulointerstitial*: - interstitial fibrosis - tubular atrophy
Each lesion is graded on a scale of 0 to 3	

During the progression of the disease, the histological type may change, passing from one class into another. Histological transformation is present in 20-30 per cent of the cases, being a consequence of the natural development of the disease or of the therapy used. Progression from classes II and III to IV is quite common (47). Between membranous glomerulonephritis and diffuse proliferative glomerulonephritis, the disease may develop in either direction (16).

The decision of performing renal biopsy should be proceed by assessing the risks of the intervention versus the risk ensuing from an incomplete or inaccurate

diagnosis, supporting either the development of a potentially treatable disorder, or the unsubstantiated use of certain drugs with notably adverse effects.

Some authors suggest that renal biopsy should be performed in all SLE patients before initiating treatment, and histology should establish diagnosis and guide treatment. Percutaneous renal biopsy in SLE is indicated in the following cases: acute renal failure, proteinuria > 500 mg/24 hs, haematuria in the presence of any proteinuria, active urinary sediment. The relative contraindications of the intervention are: haemorrhagic diathesis, advanced disease, small kidneys (48, 49).

Severe complications of the biopsy are rare; post-puncture bleeding, requiring transfusions, was reported in maximum 6.4 per cent of the cases. The predictive factors of bleeding are: advanced renal failure, platelet disorders, low hematocrit levels (25).

One of the problems that may arise in SLE patients that require renal biopsy is chronic anticoagulant therapy. Oral anticoagulants should be discontinued and replaced with heparin, which will be neutralized before the procedure. Aspirin and others NSAIDs will also be discontinued before the intervention. Anticoagulant/antiaggregation therapy will be resumed depending on the risk of thrombosis or bleeding (it may persist up to 6 weeks post-puncture) (48).

The prognostic classification of LN was made according to the clinicobiological and histological pictures (**table 7**) (50, 51, 52).

Table no. 7: Prognostic classification of lupus nephropathy

Proliferative lupus nephropathy (class III, IV)	
Mild	- class III lupus nephritis without severe lesions (crescents, fibrinoid necrosis) and without severe clinicobiological picture (proteinuria < 3 g/24 hs, normal renal function)
Moderate	- mild lupus nephritis, without therapeutic results - class III lupus nephritis with sever lesions (crescents, fibrinoid necrosis, chronicity index > 3) or with rise in serum creatinne > 30% - class IV lupus nephritis, without severe lesions
Severe	- moderate lupus nephritis, without remission in 6-12 months - class III or IV lupus nephritis with renal insufficiency and fibrinoid necrosis or crescents > 25% of glomeruli - membranous and prliferative lupus nephritis - proliferatice lupus nephritis with chronicity index > 4 or > 3 with activity index > 10 - rapid progressive lupus nephritis
Membranous lupus nephropathy (class V)	
Mild	- proteinuria < 3 g/24 hs - normal renal function
Moderate	- proteinuria ≥ 3 g/24 hs - normal renal function

Severe	- proteinuria ≥ 3 g/24 hs - rise in serum creatinine > 30%

As immunosuppression therapy has several adverse effects, the initiation of such treatment will be based both on the clinico-biological aspect and on the histological one, also taking into account the prognostic classification of LN. Thus, mesangial LN (class I and II) has a good renal prognosis and does not require immunosuppression treatment. On the other hand, proliferative LN (class III and IV) receives corticotherapy associated with immunosuppressors (cyclophosphamide, azathioprine, mycophenolate mofetil). Resistance to the classical treatment with cyclophosphamide necessities rituximab or polyvalent immunoglobulin administration. Membranous LN requires a combined treatment (cortisone and cyclophosphamide/cyclosporine/azathioprine or mycophenolate mofetil) (53).

Histopathological study is essential in assessing any LN patient as it certified the positive diagnosis of lupus renal disease, assesses the class and degree of activity, thus providing prognostic information and guiding therapy.

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