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PARTICULARITIES OF THE EVOLUTION AND THERAPEUTIC RESPONSE IN MEN WITH SYSTEMIC LUPUS ERYTHEMATOSUS AND LUPUS NEPHRITIS

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Abstract

Aim. *The prevalence ratio of systemic lupus erythematosus in men compared to women is 1:10, with more aggressive forms in men and in children. The incidence of lupus nephritis is of 50-60% in patients with lupus.*

In this paper, we aim to report on a series of cases that include male patients who had lupus nephritis via renal biopsy and were admitted between January 2011 - December 2017, with or without other SLE manifestations. The aim is to review the particularities and the therapeutic response: age at onset, disease duration, lupus nephritis class, extra-renal organ involvement of lupus disease, paraclinical findings – proteinuria, inflammatory syndrome, renal function, therapeutic response – immunosuppressive regimens used for induction and maintenance, remission onset, remission type, number of flares, side effects of immunosuppressive therapy.

Materials and method. *We have reviewed the histopathology database of male patients with lupus nephritis revealed via renal biopsy, medical charts and the Hippocrates information system in order to collect patient data.*

Outcomes. *Out of 68 renal biopsies positive for lupus nephritis, 9 were from male patients, which reveals a 6.5:1 ratio. The average age at the time of the renal biopsy is 37. 33 years old. Lupus nephritis class - 8 out of 9 patients were class IV, 1 sample was class IV+V. The duration of the corticosteroid therapy is 6.6 years. In addition, we also reviewed the immunosuppressive agents used, the number of flares, and the side effects of the medication.*

Conclusions. *Our data are similar to the literature data.*

Keywords: *systemic lupus erythematosus, lupus nephritis, renal biopsy, immunosuppressive regimens, remission.*



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Original papers

Rezumat

Scop. *Prevalența lupusului eritematos sistemic la bărbați față de femei este de 1:10, formele fiind mai agresive în cazul bărbaților și în cazul copiilor. Incidența nefritei lupice este de 50-60% dintre pacienții cu lupus.*

În această lucrare ne-am propus să prezentăm o serie de cazuri care cuprinde pacienți de sex masculin care au prezentat nefropatie lupică la biopsia renală, internați în perioada ianuarie 2011 - decembrie 2017, cu sau fără alte manifestări de LES. Scopul este de a analiza particularitățile și răspunsul terapeutic: vârsta la debut, durata bolii, clasa de nefropatie lupică, manifestări extra-renale ale bolii lupice, tablou paraclinic - proteinurie, sindrom inflamator, funcție renală, răspuns terapeutic - scheme de imunosupresie folosite pentru inducție și menținere, intrarea în remisiune, tipul remisiunii, numărul recăderilor, efecte adverse ale terapiei imunosupresoare.

Material și metodă. *Am analizat baza de date histopatologice la pacienții de sex masculin cu nefropatie lupică la biopsia renală, foile de observație și sistemul informatic Hipocrate pentru a colecta datele pacienților.*

Rezultate. *Din 68 de biopsii renale cu rezultat de nefrită lupică, 9 sunt ale pacienților de sex masculin, ceea ce face să avem un raport de 6,5:1. Vârsta medie la momentul biopsiei renale este de 37,33 ani. În ceea ce privește clasa nefropatiei lupice, 8 din 9 pacienți au avut clasa IV, o probă fiind clasele IV+V. Durata terapiei cu corticosteroizi este de 6,6 ani. De asemenea, am analizat imunosupresoarele folosite, numărul recăderilor, efectele adverse ale medicației.*

Concluzii. *Datele noastre sunt asemănătoare celor din literatură.*

Cuvinte cheie: *lupus eritematos sistemic, nefrită lupică, biopsie renală, imunosupresoare, remisiune.*

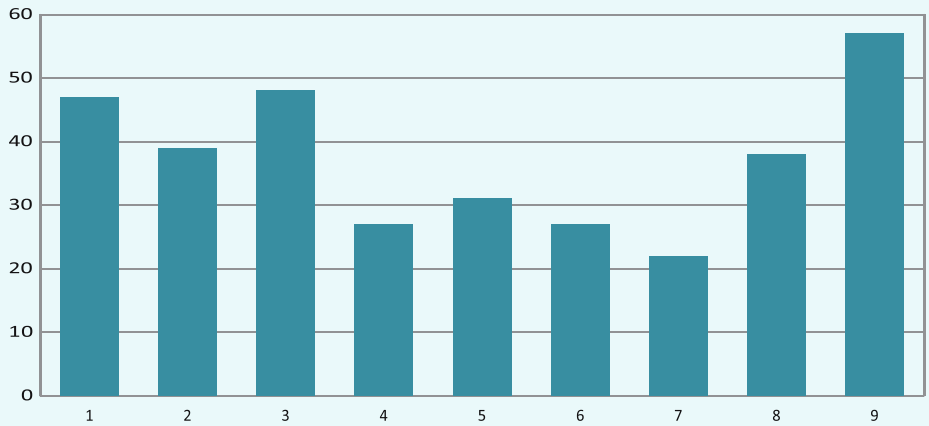


Figure 1. *Age at diagnosis*

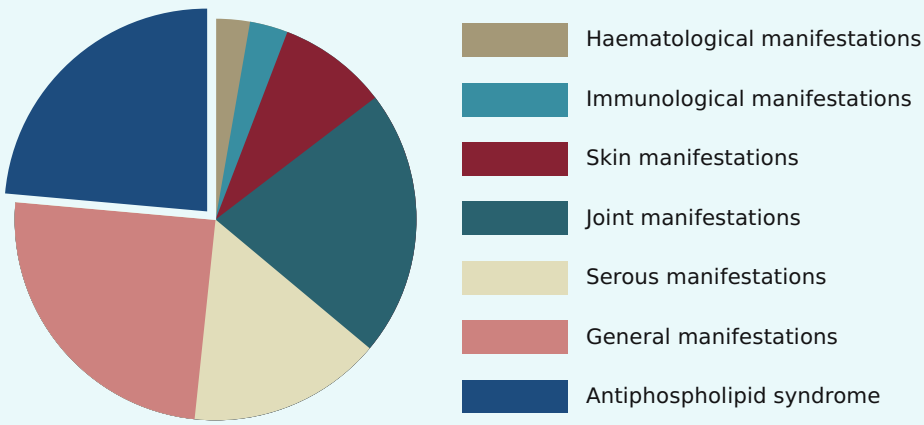


Figure 2. *Extrarenal manifestations*

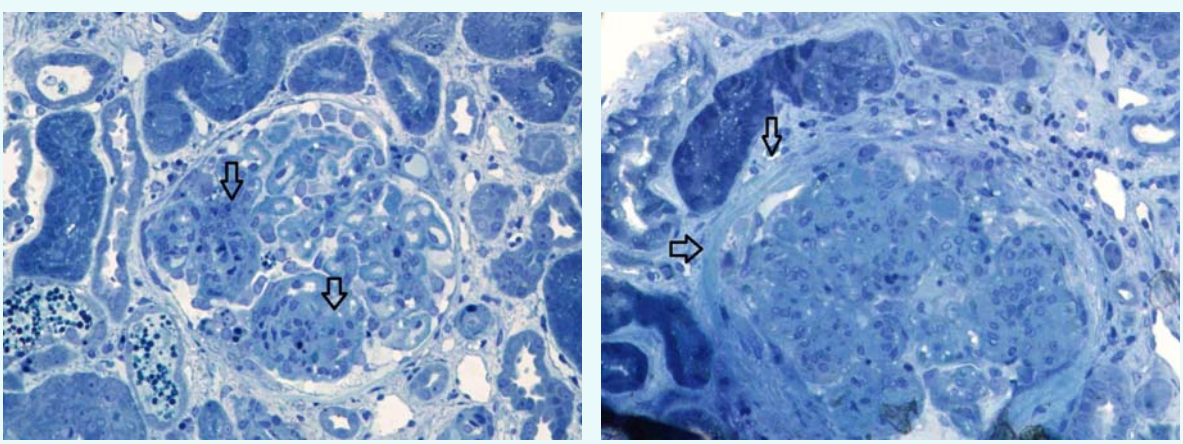


Figure 3. *Aspects of renal biopsy under optical microscope and electronic microscope: a. aspect under optical microscope, Toluidine blue staining, 20X magnification – the view shows a glomerule with mesangial and capillary proliferation, marked lobulation (black arrows), free capillary loops, with thickened walls and membrane deposits, with red blood cells in some tubes, b. aspect of lupus under optical microscope showing diffuse mesangial and capillary proliferation, with marked lobulation, the same staining and magnification – Toluidine blue, 20X (the black arrow marks Bowman's capsule)*



Introduction

Systemic lupus erythematosus is an autoimmune condition which evolves into chronic disease, and which can involve any system organ class. One of the most important criteria is the presence of the antinuclear autoantibodies – ANA. The clinical presentation is extremely diverse, ranging from constitutional symptoms, fatigue, polyarthralgias, acute and subacute cutaneous lupus lesions, alopecia, to kidney damage, haematological damage and damage to the central nervous system, and psychiatric manifestations. The criteria for disease classification help to classify patients and establish the diagnosis.

The new criteria include the mandatory presence of antinuclear autoantibodies (ANA)[1], as well as additional criteria for lupus classification, according to the system organ class, each being scored from 2 to 10 points.

A total scoring for the patient is calculated.

The prevalence ratio of systemic lupus erythematosus in men compared to women is 1:10, with the maximum incidence during childbearing age, with a similar incidence during prepuberty 4:5, with more aggressive forms in men and in children[2].

Lupus incidence is 50-60%; we know that 50-60% of lupus patients also have lupus nephritis, and there are histopathological changes, even if there are no clinical or paraclinical manifestations, the so-called "silent lupus nephritis"[3]. The presence of this visceral impairment increases mortality. Increasingly refined and specific immunosuppressive therapies, culminating in biologic therapies, have led to the increased patient survival; however, 10% of patients reach an end-stage renal disease (ESRD)[4]. Lupus nephritis incidence is higher in Afro-Americans and Hispanics, these also showing a more accelerated evolution of the loss of renal function[5]. The therapeutic response varies between men and women.

Aim and objectives

In this paper, we aim to report on a series of cases that include male patients who had lupus nephritis via renal biopsy, who underwent renal biopsy and were admitted between January 2011 - December 2017, with or without other SLE manifestations. The aim is to review the particularities and the therapeutic response. The objectives are: to present the age at onset, disease duration, lupus nephritis class, extra-renal organ involvement of lupus disease, paraclinical findings – proteinuria, inflammatory syndrome, renal function, therapeutic response – immunosuppressive regimens used for induction and maintenance, remission onset, remission type, number of flares, side effects of immunosuppressive

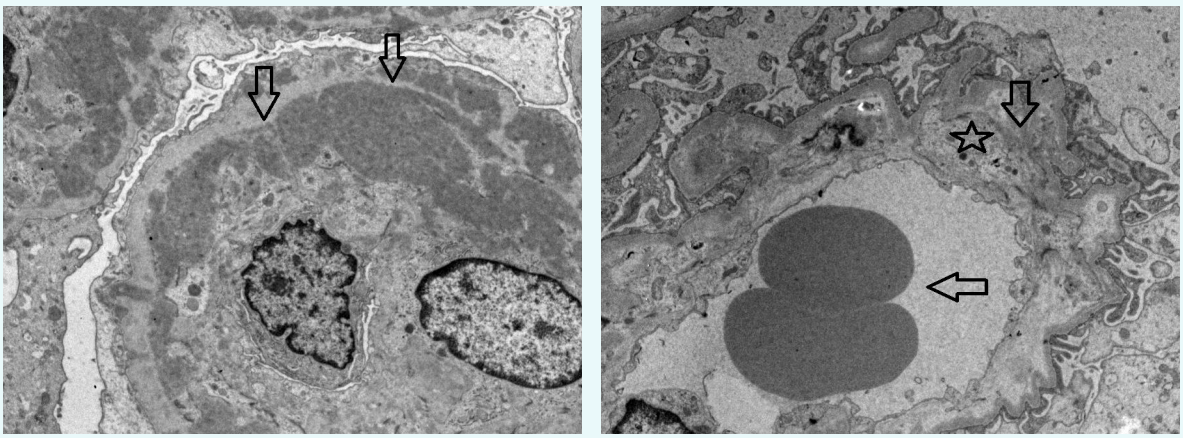


Figure 3. *Aspects of renal biopsy under optical microscope and electronic microscope: c. under electronic microscope – thick subendothelial (marked by black arrows) and membrane deposits, aspect of endothelial swelling and wire-loop capillaries, consistent with the aspect of lupus nephropathy class 4+5, d. capillary loop with marked endothelial insudation and endothelial detachment (the simple black arrow indicates 2 agglutinated red blood cells in the glomerule capillary loop), with mesangial cell interposition (the black arrow with the star sign).*

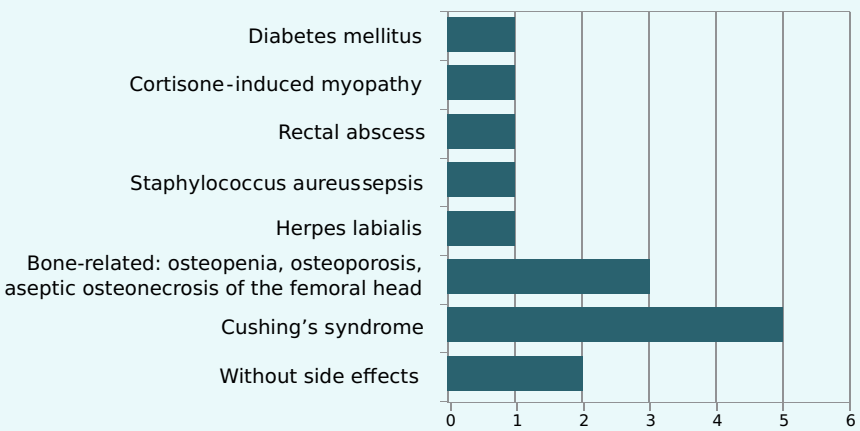


Figure 4. *Cortisone therapy side effects: the number of cases which experienced the respective complications is marked on the horizontal axis, to the right*

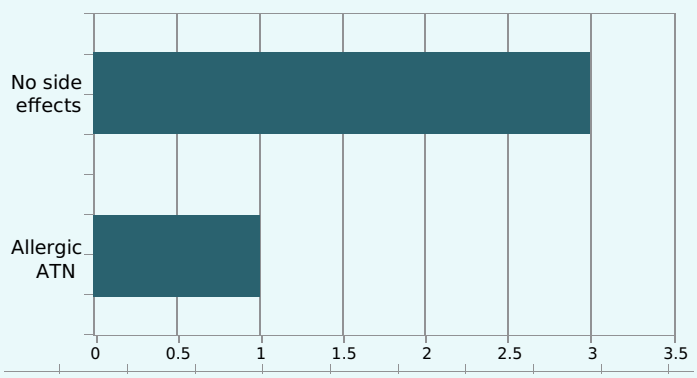


Figure 5. *Adverse reactions to azathioprine maintenance therapy.*



therapy. We compared these outcomes with the literature data.

Outcomes

Out of 68 renal biopsies positive for lupus nephritis, across different histology classes, 9 samples were from male patients, which reveals a 6.5:1 ratio . Literature data indicate a ratio of 2:1 up to 15:1 between female patients and male patients, with a maximum ratio at childbearing age[6]. The incidence in our cohort is, therefore, an average mean compared with the values reported in literature.

Systemic lupus erythematosus is a rare occurrence in male patients In the series of cases we are reporting on, the literature includes authors who found an increased incidence of lupus in men during the 5th and up to the 7th decade of life while in women, the highest incidence of lupus occurs during the 3rd and up to the 7th decade of life. The average age, across our cohort, at the time of the renal biopsy is 37. 33 years, which is close to the literature data (Figure 1). Among the extrarenal involvement, most patients experienced haematological and immunological impairment (8 out of 9 patients), joint manifestations (7 out of 9 cases) and skin manifestations (5 out of 9 cases), a minority of patients showing serous impairment (2 out of 9 cases), general manifestations occurring in only one case out of 9, while the antiphospholipid syndrome also occurred in a single case out of 9.

As regards lupus nephritis class, 8 out of 9 patients were class IV, 1 sample was class IV+V, again - findings consistent with the ones across the literature. This shows that lupus nephritis in men is more aggressive in the histopathological forms class III, IV and mixed IV+V or III+V, as they have the poorest evolution and prognosis.

We also reviewed the duration of corticosteroid therapy until the time of assessment, which was 6.6 years. Among the side effects, the most common ones were Cushing's syndrome (5 out of 9), bone damage (3 out of 9 – osteoporosis, osteopenia, aseptic osteonecrosis of the femoral head (1 case), infectious events (3 out of 9), without side effects – 2 out of 9 patients, cortisone-induced myopathy (1 out of 9 cases), and secondary diabetes mellitus – 1 out of 9 cases.

Remission inductive therapy was based on cyclophosphamide pulse therapy, the average cyclophosphamide dose delivered was 4.04 g, 2 patients experienced leukopenia, and one patient experienced cerebral abscesses secondary to cyclophosphamide pulse therapy and required conversion to mycophenolate mofetil treatment subsequent to abscess resolution. Neurosurgery was not required,

Type of first remission	Number of patients
Complete remission	3
Partial remission	4
Without remission	2

Table 1. *Number of remissions*

Number of patients with flare	Number of flares
1	9
3	3
1	2
4	0

Table 2. *Number of flares*

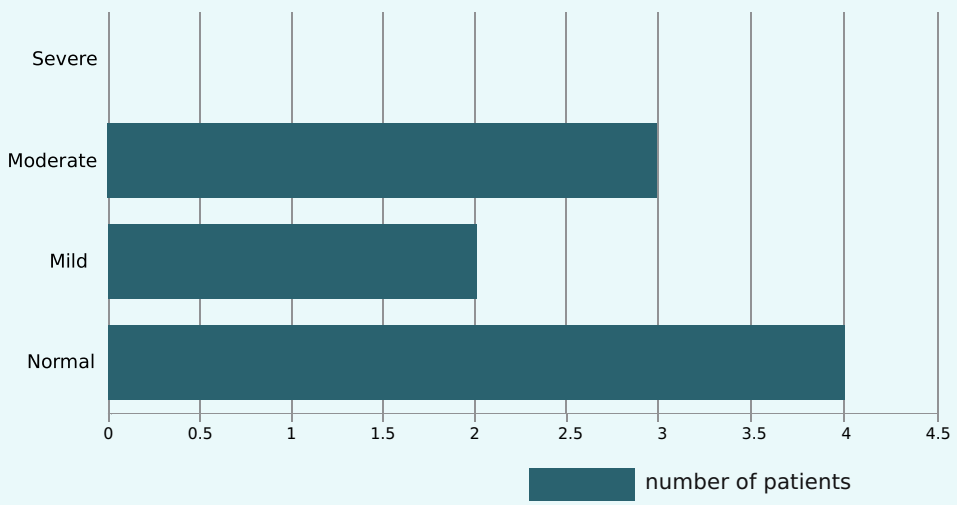


Figure 6. *The number of depression cases, following the Beck Health Questionnaire*



only antibiotic therapy. As regards maintenance therapy, 4 patients received azathioprine, out of which one experienced azathioprine-induced acute tubular necrosis (ATN), and subsequently received SoluMedrol pulse therapy, following azathioprine cessation, the renal function was recovered, and, then, the patient was switched to mycophenolate mofetil maintenance therapy. 3 patients received mycophenolate mofetil, out of which 2 patients experienced digestive side effects (flatulence, diarrhoea).

Out of the 9 patients, only 2 did not experience remission onset, the rest experienced partial remission – 4 out of 9, and complete remission – 3 out of 9 patients. The average duration until remission onset was 4.33 months since start of cyclophosphamide pulse therapy. Out of these patients, one reached the stage of renal replacement therapy via haemodialysis, while the others maintained pre-dialysis CKD. No kidney transplants were performed. When the data were examined, patients were identified with Chronic Kidney Disease stages III B -V: average serum creatinine is 2.596 mg/dL, among which 1 patient was undergoing renal replacement therapy via haemodialysis on the left radiocephalic AV fistula, average serum albumin is 4.22 g/dL, among which only 1 patient was experiencing nephritis flare, with serum albumin level of 3.4 g/dL. The average proteinuria is 2.12g/24h.

We applied the Beck Health Questionnaire to the 9 patients, and obtained the following results: 4 patients reported normal levels, 2 patients reported mild depression, 3 patients reported moderate depression, and none of the patients reported severe depression.

Conclusions and Discussions

Systemic lupus erythematosus is a rare occurrence in male patients; studies cite a 2:1 ratio during the pre-childbearing age, up to 9:1 between men and women[6, 7], with a maximum ratio of 15:1 in some studies[8]; in our cohort there was a ratio of 6.5:1 between male and female patients, perhaps also because male patients may be more reluctant to accept a renal biopsy, or because they may delayed check-up visits in comparison with female patients.

In the 9-cases series that we report on, we reviewed the specific characteristics of patient evolution, therapy and therapeutic response, and compared them with the ones in literature. Our outcomes are similar to the ones reported for Caucasian patients, but we also found different outcomes, which we shall now present in detail: male patients with lupus report arthralgia and arthritis more rarely than female patients in most recent studies (with the exception of studies

on Turkish populations, where men reported these symptoms more commonly)[9]; in our lot of patients, 7 out of 9 experienced arthralgia.

Also among the rarer manifestations in men are photosensitivity, malar rash, oral ulcers, alopecia and the Raynaud syndrome, except for alopecia – 2 cases, and photosensitivity (2 cases), the rest of the patients did not report any of these symptoms.

However, in literature, male patients report more commonly discoid lesions, subacute cutaneous lesions, serositis, renal impairment, fever, weight loss, myositis, lymphopenia, and haemolytic anaemia, central nervous system manifestations being reported in a controversial manner across current studies[10,11,12,13,14].

In our patient lot, the most common manifestations were haematologic manifestations – 8 out of 9 cases, immunological manifestations – 8 out of 9 cases, arthralgia – 7 out of 9 cases, cutaneous lesions – 5 out of 9 cases, serositis – 3 out of 9 cases (although literature cites them as mostly occurring in men), general manifestations asthenia , fever – 1 out of 9 patients, antiphospholipid syndrome – 1 out of 9 patients, again - in contrast to the literature data, where thrombosis is more commonly reported in male patients than in female patients.

Also, male patients report renal impairment more commonly, as well as being hypertensive, which aggravates the renal prognosis. Thus, some studies show that male patients with lupus have a high risk of chronic organic lesions and a shorter survival. The LUMINA study found an association between the risk of early organ injury and the male gender[15]. Other authors from China[16], Greece[17], or Latin America[18] have not found this link. In the Hopkins lupus cohort, an association between the male gender and organ lesions, such as seizures, myocardial infarction, angina pectoris, thrombosis, and renal damage, was found[19]. Renal and cardiovascular impairment were associated to the male gender in studies conducted in Asia and Latin America[20,21].

As regards the mortality data, these are a matter of controversy: higher mortality in male patients was cited in studies carried out in Germany, Toronto, Hopkins, and Duke's[20, 21]. The data from Great Britain[22] and Latin America[18] have not confirmed this link. The idea of phenotypic differences in systemic lupus erythematosus according to patient gender being caused by a different genetic load, namely ethnicity, is controversial[23,24].

As regards prognosis, patients with remission, either complete or partial, have a better renal survival rate compared to the patients who do not achieve remission[25, 26,27]. Our data are consistent in this aspect, most patients having achieved partial remission (4 out of 9 patients) and complete remission (3 out of 9 patients), and 2 out of the 9 patients who did not show any remission onset, out of which only 1 patient was undergoing renal function replacement therapy via haemodialysis, while the other patients were classified pre-dialysis CKD stages III B – V. The limits of the paper we submit for review are the small group of patients – respectively, a series of cases, the fact that we report data from a single university centre, which render the outcomes difficult to extrapolate to the general male lupus population. We are waiting for new data and shall further study this topic, aiming to provide information on a rarer patient category: men with systemic lupus erythematosus and lupus nephritis. We also wish to specify that patients were referred to the clinic for renal biopsy either by fellow rheumatologists – a minority –, either



by internal medicine and family medicine fellow physicians, who detected nitrogen retention, nephrotic syndrome and hypertension, referring these patients to us for further nephrology examinations.

Thus, neither do we have data on the male lupus patients treated by fellow rheumatologists who did not report the renal involvement as an initial manifestation, or who did not experience clinical and paraclinical renal manifestations, nor do we have data on "silent nephritis", thus on male patients, as biopsies were collected in the clinic solely for the patients with nephrological manifestations: active urinary sediment, nitrogen retention, hypertension, nephrotic syndrome, and for which other nephrological causes were initially suspected, other glomerular diseases.

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