AUCTORES
Globalize your Research

International Journal of Clinical Case Reports and Reviews
Marilena Stoian*

Open Access

Case Report

A Clinical Approach of Lupus Nephritis Associated with Catastrophic Antiphospholipid-Antibody Syndrome Review and Case Report

Marilena Stoian*

Internal Medicine and Nephrology, Carol Davila University Of Medicine, Bucharest, Romania

Ion Cantacuzino Hospital, Bucharest, Romania

Corresponding Author: Marilena Stoian, I. Cantacuzino Hospital, Clinic of Internal Medicine, Bucharest, Romania.

Received Date: July 04 2022 | **Accepted Date:** August 08 2022 | **Published Date:** September 27 2022

Citation: Stoian M. (2022). A Clinical Approach of Lupus Nephritis Associated with Catastrophic Antiphospholipid-Antibody Syndrome Review And Case Report. *International Journal of Clinical Case Reports and Reviews*. 12(1); DOI:10.31579/2690-4861/237

Abstract

Glomerulonephritis is a major cause of morbidity in systemic lupus erythematosus (SLE). In fact, immune complex formation and deposition in the kidney results in intraglomerular inflammation with recruitment of leukocytes, and activation and proliferation of resident renal cells. Intense injury may destroy resident renal cells by necrosis or apoptosis resulting in fibrinoid necrosis. When injury is less intense, endocapillary cells respond by proliferating and production of extracellular matrix (proliferative lesions). Renal biopsy, examination of urine sediment and measurement of C3 levels (and to less anti-DNA titers) are essential for the management of lupus nephritis. Treatment depends on the severity of the lupus nephritis. Disease severity depends on the presence or absence of high-risk factors. These include demographic (male gender, black race), clinical (failure to achieve response or marked delay in response, multiple relapses, pregnancy), laboratory (impaired renal function, severe anemia with hematocrit less than 26%) and histologic features (mixed membrane- proliferative or proliferative nephritis; cellular crescents and/or fibrinoid necrosis; cellular crescent and/or fibrinoid necrosis; and moderate to high degrees of interstitial fibrosis and/or tubular atrophy).

Keywords: systemic lupus erythematosus; renal cells; renal biopsy

Introduction

Glomerulonephritis is a major cause of morbidity in systemic lupus erythematosus (SLE). In fact, immune complex formation and deposition in the kidney results in intraglomerular inflammation with recruitment of leukocytes, and activation and proliferation of resident renal cells. Intense injury may destroy resident renal cells by necrosis or apoptosis resulting in fibrinoid necrosis. When injury is less intense, endocapillary cells respond by proliferating and production of extracellular matrix (proliferative lesions). Renal biopsy, examination of urine sediment and measurement of C3 levels (and to less anti-DNA titers) are essential for the management of lupus nephritis. Treatment depends on the severity of the lupus nephritis. Disease severity depends on the presence or absence of high-risk factors. These include demographic (male gender, black race), clinical (failure to achieve response or marked delay in response, multiple relapses, pregnancy), laboratory (impaired renal function, severe anemia with hematocrit less than 26%) and histologic features (mixed membrane- proliferative or proliferative nephritis; cellular crescents and/or fibrinoid necrosis; cellular crescent and/or fibrinoid necrosis; and moderate to high degrees of interstitial fibrosis and/or tubular atrophy).

Antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterized by thrombotic episodes in the arterial or venous circulation, in the presence of antiphospholipid antibodies (aPL), namely lupus anticoagulant (LA), anticardiolipin antibodies, and anti-β2glycoprotein-I antibodies (anti-β2GPI) [1]. APS can be either primary or secondary when it occurs in the context of other underlying autoimmune disorder, mainly systemic lupus erythematosus (SLE). aPL positivity may occur in 0–5% of healthy individuals and in approximately 30–40% of patients with SLE; one third of SLE patients with positive aPL develop thrombosis during their follow-up. Antiphospholipid syndrome can affect any part of kidney vasculature such as renal arteries and veins, intrarenal arteries and arterioles, and glomerular capillaries [2]. In addition to thrombotic manifestations from the large renal vessels that are part of the updated Sapporo criteria for APS, characteristic microvascular nephropathy lesions are included in the non-criteria manifestations of APS [1,2].

Lupus nephritis and antiphospholipid syndrome

Kidney damage is a well-recognized complication of the antiphospholipid syndrome (APS), either primary or systemic lupus erythematosus (SLE)-

associated APS. Kidney involvement in APS involves a variety of manifestations, such as renal artery thrombosis or stenosis, renal vein thrombosis, allograft loss due to thrombosis after kidney transplantation, and injury to the renal microvasculature, also known as APS nephropathy. Biopsy in patients with APS nephropathy includes acute thrombotic microangiopathy lesions and chronic intrarenal vascular lesions such as interlobular fibrous intimal hyperplasia, arterial and arteriolar recanalizing thrombosis, fibrous arterial occlusion, and focal cortical atrophy. The most frequent clinical features are hypertension, microscopic hematuria, proteinuria (ranging from mild to nephritic levels), and renal insufficiency. It is uncertain whether antiphospholipid antibodies or other factors are implicated in the development of APS nephropathy, and whether it is driven mainly by thrombotic or by inflammatory processes. Experimental models and clinical studies of thrombotic microangiopathy lesions implicate activation of the complement cascade, tissue factor, and the mTORC pathway. Currently, the management of APS nephropathy relies on expert opinion, and consensus is lacking. There is limited evidence about the effect of anticoagulants, and their use remains controversial. Treatment approaches in patients with APS nephropathy lesions may include the use of heparin based on its role on complement activation pathway inhibition or the use of intravenous immunoglobulin and/or plasma exchange. Targeted therapies may also be considered based on potential APS nephropathy pathogenetic mechanisms such as B-cell directed therapies, complement inhibition, tissue factor inhibition, mTOR pathway inhibition, or anti-interferon antibodies, but prospective multicenter studies are needed to address their role. aPL positivity is a poor prognostic factor in lupus nephritis [3,4]. In a study of 111 SLE patients with nephritis and a mean follow-up of 14 years, the presence of positive aPL (p = 0.02) was identified as independent predictor of chronic renal function deterioration (5). Natejumnong et al. showed that patients with SLE nephritis and LA positivity had higher systolic blood pressure (133.7 versus 121.9 mmHg, p = 0.005), serum creatinine (233.0 versus 94.9 μmol/L), and 24-h urine protein excretion (2.6 versus 1.4 g, p = 0.02), features associated with worse renal prognosis [6]. However, in other lupus nephritis studies, aPL did not correlate with long-term kidney function [7,8] or even showed a protective effect against renal damage [9]. It was demonstrated an association between aPL and a variety of intrarenal vascular lesions in kidney biopsies of patients with lupus nephritis [10]. Thrombotic microangiopathy in glomeruli and/or renal arterioles was the most common lesion, characterized by fibrin thrombi without inflammatory cells or immune complexes [11,12]. Several studies from the early 1990s have examined the impact of aPL-associated intrarenal vascular lesions on long-term outcomes of SLE patients [10-14]. In 2013, Song et al. reported that thrombotic microangiopathy in patients with lupus nephritis was an independent predictor of poor renal outcome (HR: 2.772, 95% CI 1.009–7.617, p = 0.048) [15]. Wu et al. showed that thrombotic microangiopathy lesions in lupus nephritis was associated with worse renal prognosis compared to other vascular lesions and suggested that vasculopathy be included in ISN/RPS classification system to increase its predictive value for renal outcomes [16].

Catastrophic APS (CAPS) is a very rare (<1%) and extremely severe variant of APS. It is characterized by multiple systems and thrombotic organ involvement that occurs in a very short period (days to weeks). Renal involvement is a common feature in CAPS, the most frequent finding is thrombotic microangiopathy TMA, but other chronic lesions of APSN can also be found [17]. The treatment of CAPS includes high dose steroids, anticoagulation, IV Immunoglobulin, and plasma exchange. In patients with CAPS associated with SLE, cyclophosphamide may be effective. Moreover, eculizumab has been successfully used in few cases.

Case report

A 32-year-old woman was admitted to the hospital with rapidly worsening renal function. For twelve years ago she was diagnosed with systemic lupus erythematosus, manifested by Raynaud s syndrome, thoracic and abdominal serositis, rash, and livedo reticularis. Ten years ago, the antiphospholipid -antibody syndrome was diagnosed. More recently she had two successful pregnancies. Aspirin had been prescribed and prednisone, hydroxychloroquine, and omeprazole. Several weeks before admission, arthralgia of increasing severity develops, with a more extensive rash and with vomiting and pleuritic pain, which was more severe in the right side of the chest and in the epigastrium. In addition, there was progressive digital ischemia, prominent nasal cyanosis, and a new painful rash associated with discontinuation of acenocumarol. The dose of prednisone was raised from 20 mg to 60 mg daily, and the arthralgia and rash improved. Four days before admission, vomiting developed, with worsening epigastric pain that radiated to the back.

On admission, the temperature was $36{,}4^0$ C, the pulse was 60, and the respiration rate was 20/minute; the blood pressure was 140/80 mm. The patient has an BMI: 36- means grade 2 obesity, erythematous rash on her face and anterior torso, and there was a popular rash on the left hand that blanched with compression. Cyanosis was evident on the tip of the nose and on the left hand. Livedo reticularis was present on the nose and the fingers, without active ulcers. Abdominal examination revealed epigastric tenderness without rebound tenderness. There was no evidence of active synovitis, and neurologic examination showed no abnormalities.

The urine was positive for protein; the sediment contained 2 to 4 red cells per high-power field, without white cells or casts. Hematologic, serologic and blood chemical lab values are given in Tables 1,2, and 3. Pulse oximetry indicated that the oxygen saturation was 98 percent while the patient was breathing ambient air. The findings on an electrocardiogram were normal. Radiographs of the chest showed subsegmental atelectasis or scarring at the base of the left lung and slight enlargement of the heart. An ultrasound examination revealed normal -appearing kidneys, 10.5 cm in length.

VARIABLE	DAY 1	DAY 2	DAY 3	DAY 4
Hematocrit	35.2	29.5	31.2	31.2
Mean corpuscular volume	88			
Erythrocyte sedimentation rate	3			
Reticulocyte count%			1.0	
White cell count	10000	5100	6800	7000
Neutrophils	77	86		90
Platelet count	98.00	56	64	58
Prothrombin time	normal			normal
Partial-thromboplastin time	normal			normal

Table 1. *Hematologic Laboratory Values*

VARIABLE	DAY 1	DAY 2	DAY 3	DAY 4
Protein	8.2			8,0
LDH		Normal		
Alkaline phosphatase	143	110	108	108
Aspartate aminotransferase	Normal	Normal	Normal	Normal
Alanine aminotransferase	Normal	Normal	Normal	Normal
Urea nitrogen(mg/dl)	32	26	27	35
Creatinine(mg/dl)	1,2	1.7	2.3	3.1
Sodium (mmol/liter)	135		135	
Potassium (mmol/liter)	3.9		4.7	
Chloride (mmol/liter)	108		109	
Carbon dioxide (mmol/liter)	17		19	
Bilirubin	Normal	Normal	Normal	Normal
Amylase	Normal			Normal

Table 2.*Blood Chemical Values*

TEST	VALUE
Antinuclear antibody	1:80
Anti-DNA	1:320
Anti-Sm antibody	200
Anti-U1-RNP antibody	195
Anticardiolipin antibody	
IgG	53
IgM	16
Serologic test for syphilis	Negative
Anti-Ro antibody	Negative
Anti-La antibody	Negative
Direct Coombs test	Negative

Table 3. *Results of Serologic Tests*

Treatment with prednisone (60 daily) was continued, fluids and electrolytes were infused intravenously, and paracetamol was given for pain. The epigastric and right-sided chest pain diminished, but the joint pain persisted. Microscopical examination of biopsy specimens of the gastric antrum and the duodenum by esophagogastroduodenoscopic examination showed mild, nonspecific chronic inflammation; Helicobacter pylori was not detected. On the third hospital day, treatment with prednisone was discontinued, and intravenous administration of methylprednisolone was begun. Examination of a blood smear showed no evidence of the hemolytic-uremic syndrome or of thrombotic thrombocytopenic purpura. Antiphospholipid-antibody syndrome causing acute renal failure and systemic lupus erythematosus was the clinical diagnoses which confirmation needed a diagnostic procedure; so, on the fourth day, was performed a kidney biopsy with histopathological exanimation. (Figure 1, Figure2)

Discussions

The patient had a history of Raynaud s syndrome and serositis and had positive tests for antinuclear, anti-DNA, anti-Sm, and anti-UI-RNP antibodies. A positive test for antinuclear, anti-DNA, anti-Sm, and anti-UI-RNP antibodies, though about 90 percent sensitive for systemic lupus erythematosus, is only about 70 percent specific, yielding positive results for a variety of other diseases. In this patient, the test for anti-DNA antibody, which indicated a dilution of 1:320, is more specific, though less sensitive, for systemic lupus erythematosus than the test for antinuclear antibodies (18). It may even have some correlation with disease activity, since in about 90 percent of patients with highly active systemic lupus erythematosus and nephritis this test is positive. (19). Many of the previous clinical findings in this patient and her apparent response to prednisone are also consistent with the diagnosis of *systemic lupus erythematosus*, which appears to be well founded.

The antiphospholipid-antibody syndrome is caused by autoantibodies to proteins bound to negatively charged phospholipids. Two of the most common targets for the so-called antiphospholipid antibodies are prothrombin, which forms complexes with phospholipids, and β_2 glycoprotein I (20). The so- called lupus anticoagulant is manifested as a prolongation in the activated partial- thromboplastin time that is not corrected by the addition of normal plasma. The patient of our case report had elevated titers of antiphospholipid antibodies in the form of anticardiolipin IgG and had a slight elevation in the titer of anticardiolipin IgM. Since she did not have a prolonged activated partial- thromboplastin time, there is no evidence of lupus anticoagulant. The clinical hallmark of the antiphospholipid-antibody syndrome is the presence of vascular venous and arterial thromboses. Thrombocytopenia is common, and in the kidneys, the presence of microthrombi in the glomeruli and small arteries is manifested as thrombotic microangiopathy similar to that in the hemolytic -uremic syndrome. The patient of our case report had a history of postpartum pulmonary embolus, fingertip ulcers, and

thrombocytopenia: on these clinical and serological findings, the diagnosis of *the lupus-associated antiphospholipid-antibody syndrome* also seems firmly established.

Which of these diseases is predominantly responsible for the patient s acute illness, characterized by epigastric and chest pain, rash, cyanosis of the fingers and nose, livedo reticularis, joint pain, and rapidly advancing renal failure? The discontinuation of the acenocumarol four months before admission and the ischemic changes in the skin and fingers point to the antiphospholipid-antibody syndrome. The rashes, arthralgias, and improvement with prednisone high dose are more characteristic of systemic lupus erythematosus. The abdominal and chest pain and vomiting, the normal result on liver- function tests, the normal amylase and lipase levels, the normal findings on ultrasound image of the abdomen, and the absence of gastrointestinal bleeding may reflect either mild ischemic changes in the bowel due to the antiphospholipid-antibody syndrome or serositis associated with systemic lupus erythematosus.

The patient s rapidly progressive renal failure may be associated with either the antiphospholipid-antibody syndrome or systemic lupus erythematosus. In the antiphospholipid-antibody syndrome, microthrombi form in glomerular capillaries and small arteries, with intimal thickening and subintimal deposition of thrombin in the absence of marked inflammatory changes or immune-complex deposits; occasionally, thromboses are also found in larger renal arteries and veins. The urine sediment typically contains few cells or casts, and the level of proteinuria ranges from mild to nephrotic. By contrast, in cases of severe lupus nephritis there are numerous immune complex deposits in glomeruli and occasionally in arterioles, accompanied by inflammation. The urine sediment is active, containing cells and casts, and there is marked proteinuria. Progression of severe renal failure over a period of a few days demonstrated that the antiphospholipid-antibody syndrome predominant and it was the chief cause rapidly progressive renal failure.

The differential diagnosis is very important because therapy for the two conditions differs considerably. For the antiphospholipid-antibody syndrome, therapy consists of anticoagulation, which is usually begun with heparin and then changed to acenocumarol at doses sufficient to maintain a normalized ratio of 3 or higher. Plasmapheresis has sometimes been recommended to remove the anticardiolipin antibodies. Therapy for active systemic lupus erythematosus include administration of corticosteroids and other immunosuppressive agents. Examination of a **kidney-biopsy** specimen should easily distinguish between these two disorders. The most important abnormality was the presence of numerous recent thrombi in medium-sized arteries, arterioles, and glomerular capillaries. Some of the thrombosed arteries and arterioles were characterized by fibrous and edematous intimal thickening, but there was no leukocytic infiltration or fibrinoid necrosis of the vessel walls. (Figure 1)

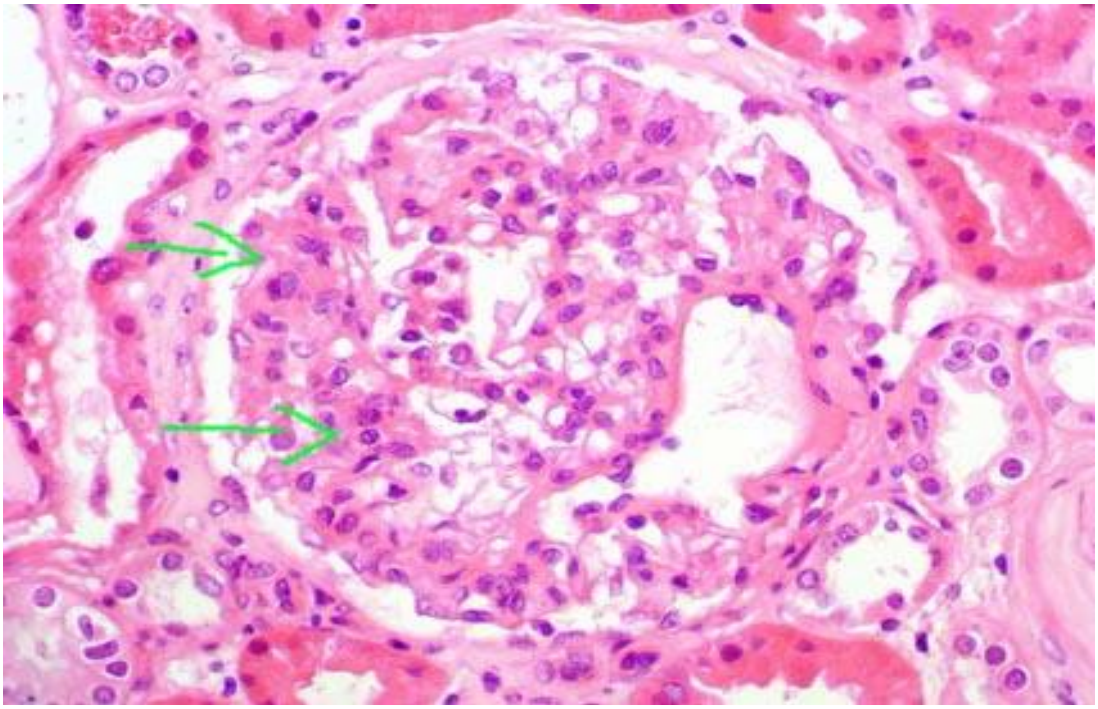

Figure 1. *Glomerular tuft with proliferation of mesangial cells, segments with endocapillary proliferation, and a small, circumscribed crescent (arrow). In lupus nephritis active proliferation and glomerular changes are frequently segmental; nevertheless, to determine if it is class III (focal) or IV (diffuse) it is necessary to quantify the percentage of glomeruli with lesions (H&E, X400).*

Most of the glomeruli contained extensive intracapillary thrombi, associated with necrosis and loss of most or all the intrinsic glomerular cells. (Figure 2)

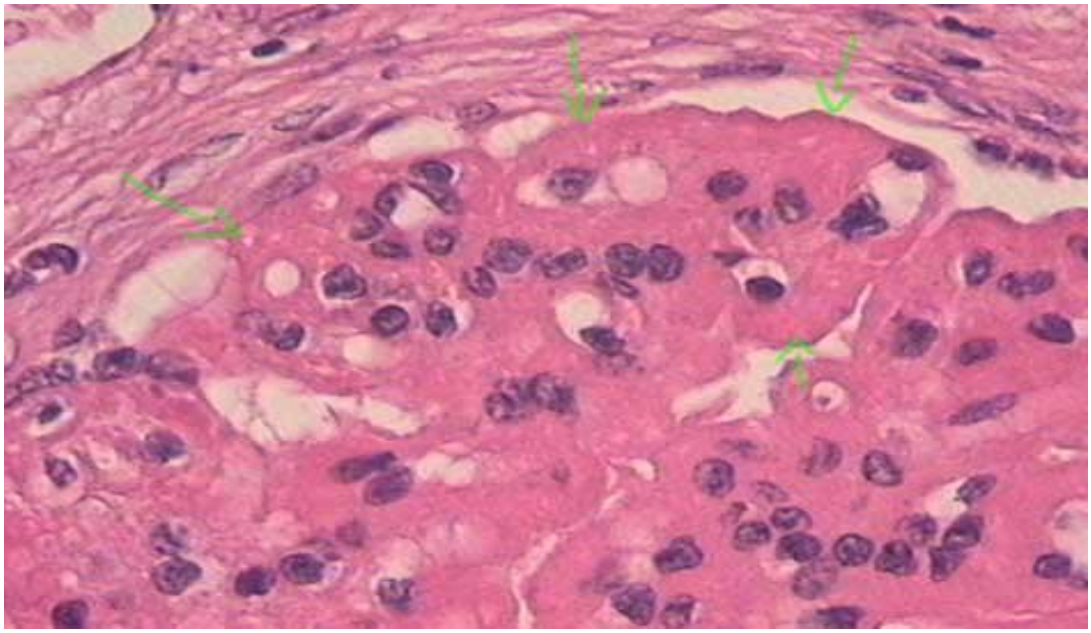

Figure 2. *Deposits thickening capillary walls and hyaline thrombi (blue arrows) that correspond to immune aggregates in capillary lumina; they have, although often non-visible, connection with subendothelial deposits and they are not true thrombi. These deposits, demonstrated by light microscopy, indicate class IV lupus nephritis. Many of these deposits are seen as wire loops with H&E stain. (H&E, X400)*

In a few glomeruli, the most striking feature was the presence of agglutinated red cells, which had occluded capillary lumina. Foci of tubular necrosis and scattered interstitial mononuclear -cell infiltrates were also present. Microscopical examination by immunofluorescence revealed fibrillar staining for fibrin in arterioles and glomerular capillaries, indicating the presence of true thrombi rather than the so-called hyaline thrombi, which are composed principally of immune complexes and are commonly found in active proliferative lupus nephritis. (21). All the abnormalities of renal biopsy are mainly those of thrombotic microangiopathy. This term does not denote a disease entity but rather a pathologic process that occurs in several conditions, including the hemolytic-uremic syndrome, thrombotic thrombocytopenic purpura, malignant hypertension, scleroderma, and the antiphospholipid-antibody syndrome.

Conclusion

Based on clinical and morpho pathological findings the diagnosis in this clinical case is the antiphospholipid-antibody syndrome due to systemic lupus erythematosus.

References

1. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. (2006) International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost* 4(2):295–306.
2. Tektonidou MG. Renal involvement in the antiphospholipid syndrome (APS)-APS nephropathy. *Clin Rev Allergy Immunol* (2009) 36(2–3):131–40.
3. Abu-Shakra M, Urowitz MB, Gladman DD, Ritchie S. (1996) The significance of anticardiolipin antibodies in patients with lupus nephritis. *Lupus* 5(1):70–73.
4. Bhandari S, Harnden P, Brownjohn AM, Turney JH. (1998) Association of anticardiolipin antibodies with intraglomerular thrombi and renal dysfunction in lupus nephritis. *QJM* 91(6):401–409.
5. Moroni G, Ventura D, Riva P, Panzeri P, Quaglini S, Banfi G, et al. (2004) Antiphospholipid antibodies are associated with an increased risk for chronic renal insufficiency in patients with lupus nephritis. *Am J Kidney Dis* 43(1):28–36.
6. Natejumnong C, Ruangkanchanasetr P, Aimpun P, Supaporn T. (2006) Significance of antiphospholipid antibodies in lupus nephritis. *J Med Assoc Thai* 89(Suppl 2): S121–128.
7. Frampton G, Hicks J, Cameron JS. (1991) Significance of anti-phospholipid antibodies in patients with lupus nephritis. *Kidney Int* 39(6):1225–1231.
8. Parodis I, Arnaud L, Gerhardsson J, Zickert A, Sundelin B, Malmström V, et al. (2016) Antiphospholipid antibodies in lupus nephritis. *PLoS One* 11(6): e0158076.
9. Mehrani T, Petri M. (2011) IgM anti-beta2 glycoprotein I is protective against lupus nephritis and renal damage in systemic lupus erythematosus. *J Rheumatol* 38(3):450–453.
10. Appel GB, Pirani CL, D'Agati V. (1994) Renal vascular complications of systemic lupus erythematosus. *J Am Soc Nephrol* 4(8):1499–1515.
11. Farrugia E, Torres VE, Gastineau D, Michet CJ, Holley KE. (1992) Lupus anticoagulant in systemic lupus erythematosus: a clinical and renal pathological study. *Am J Kidney Dis* 20(5):463–471
12. Hughson MD, Nadasdy T, McCarty GA, Sholer C, Min KW, Silva F. (1992) Renal thrombotic microangiopathy in patients with systemic lupus erythematosus and the antiphospholipid syndrome. *Am J Kidney Dis* 20(2):150–158.
13. Bridoux F, Vrtovsnik F, Noël C, Saunier P, Mougenot B, Lemaitre V, et al. (1998) Renal thrombotic microangiopathy in systemic lupus erythematosus: clinical correlations and long-term renal survival. *Nephrol Dial Transplant* 13(2):298–304.
14. Zheng H, Chen Y, Ao W, Shen Y, Chen XW, Dai M, et al. (2009) Antiphospholipid antibody profiles in lupus nephritis with glomerular microthrombosis: a prospective study of 124 cases. *Arthritis Res Ther* 11(3): R93.
15. Song D, Wu LH, Wang FM, Yang XW, Zhu D, Chen M, et al. (2013) The spectrum of renal thrombotic microangiopathy in lupus nephritis. *Arthritis Res Ther* 15(1): R12.

16. Wu LH, Yu F, Tan Y, Qu Z, Chen MH, Wang SX, et al. (2013) Inclusion of renal vascular lesions in the 2003 ISN/RPS system for classifying lupus nephritis improves renal outcome predictions. *Kidney Int* 83(4):715–723.
17. Tektonidou MG, Sotsiou F, Moutsopoulos HM. (2008) Antiphospholipid syndrome nephropathy in catastrophic, primary, and systemic lupus erythematosus-related APS. *J Rheumatol* 35:1983–1988.
18. Rekvig OP, Nossent JC. (2003) Anti-double-stranded DNA antibodies, nucleosomes, and systemic lupus erythematosus: a time for new paradigms? Arthritis Rheum. 2003 Feb;48(2):300–312.
19. Hernando Monserrat, González Concepción, Sánchez Angel, Guevara Paloma, Navajo José et al. (2002) Clinical evaluation of a new automated anti-dsDNA fluorescent immunoassay. Clin Chem Lab Med. Oct;40(10):1056–1060.
20. Cervera R, Espinosa G. (2012) Update on the catastrophic antiphospholipid syndrome and the "CAPS Registry". Semin Thromb Hemost. Jun;38(4):333-338.
21. Najafi CC, Korbet SM, Lewis EJ, Schwartz MM, Reichlin M, Evans J: (2001) Significance of histologic patterns of glomerular injury upon long-term prognosis in severe lupus glomerulonephritis. Kidney Int 59: 2156–2163.

DOI: 10.31579/2690-4861/235