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CLASS IV LUPUS NEPHRITIS, THROMBOTIC MICROANGIOPATHY, AND EXTENSIVE LONGITUDINAL MYELITIS AS AN INITIAL MANIFESTATION OF SYSTEMIC LUPUS ERYTHEMATOSUS - CASE REPORT

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ABSTRACT

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease whose patients present with variable clinical features, from mild joint and skin involvement to life-threatening renal, hematologic, or central nervous system involvement. Most patients with systemic lupus erythematosus will have clinical evidence of renal disease. Antiphospholipid syndrome (APS) is the association of thrombosis and/or gestational morbidity with antiphospholipid antibodies (aPL). Thirty to forty percent of patients with systemic lupus erythematosus have positive results for aPL, which may impact the presentation, management, and prognosis of SLE. Any organ or system can be affected by APS. It may present with thrombotic microangiopathy, as has been observed in APS nephropathy. Myelitis is an inflammatory disease that manifests with rapidly progressive motor, sensory, and autonomic symptoms with catastrophic results. Neuropsychiatric manifestations (NPM) in systemic lupus erythematosus have a significant impact on the prognosis of the disease due to their frequency and severity. Myelopathy is a rare manifestation of the central nervous system (CNS) in SLE and affects 1% to 2% of patients. This case report aims to alert health professionals to the diagnosis of SLE in the general population and its main presentations, as well as its atypical and rare manifestations, such as the triple presentation of the onset of lupus demonstrated in this case: Class IV Lupus Nephritis, Thrombotic Microangiopathy, and Neuromyelitis with extensive longitudinal myelitis. Furthermore, in the literature review searching for the onset of SLE with the triple manifestation mentioned in this case, no such mentions were found.

Keywords: Systemic Lupus Erythematosus. Lupus Nephritis. Antiphospholipid Syndrome. Transverse Myelitis.

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease in which patients present with variable clinical features, ranging from mild joint and skin involvement to life-threatening renal, hematologic, or central nervous system involvement. Constitutional symptoms such as fatigue, fever, and weight loss are present in most patients with systemic lupus erythematosus (SLE) at some point during the disease course 1

SLE occurs more commonly in certain racial and ethnic groups, particularly black, Asian, and Hispanic populations, compared with white populations. It occurs primarily in young women of childbearing age. The disease presentation, clinical course, and outcome vary significantly among individuals, age groups, and ethnicities. For its diagnosis, it is necessary to fulfill the diagnostic criteria according to the European League Against Rheumatism / American College of Rheumatology (EULAR / ACR) of 2019 2,3

Most patients with systemic lupus erythematosus will have clinical evidence of kidney disease, usually an abnormal urinalysis, at some point in the course of the disease. Lupus nephritis (LN) typically develops early in the course of the disease. Clinically evident renal pathology eventually occurs in up to half of patients with SLE, and up to 10 percent of patients with LN will develop end-stage renal disease (ESRD) 4.

Thrombotic microangiopathy (TMA) describes a specific pathologic lesion in which abnormalities in the vascular wall of arterioles and capillaries lead to microvascular thrombosis. TMA is a histopathologic diagnosis made by tissue biopsy, typically a renal biopsy. It is commonly inferred from the observation of microangiopathic hemolytic anemia and thrombocytopenia in the appropriate clinical setting 5. Anticardiolipin antibodies are autoantibodies with activity directed against negatively charged phospholipids. These antibodies have been detected in the serum of patients with systemic lupus erythematosus. Anticardiolipin antibodies are considered the hallmark of antiphospholipid syndrome, a clinical entity characterized by episodes of venous and arterial thrombosis, fetal loss, thrombocytopenia, and prolonged activated partial thromboplastin time (aPTT) 6.

In SLE-associated myelitis, patients present with acute to subacute paraparesis or quadriparesis, which is usually bilateral but not always symmetric; sensory impairment localized to a spinal sensory level; and/or impairment of bowel or bladder function 7.

METHODOLOGY

About the formulation of the case report, information contained in the patient's electronic medical record stored in the GSUS of the Hospital Universitário Regional de Maringá (HUM) of the Universidade Estadual de Maringá (UEM) and data obtained from the

electronic medical record stored in the TAZY of the Hospital Santa Casa de Maringá were used. The confidentiality of the information and anonymity of the patient were respected, without including information that could allow her identification.

For the literature review, a search was carried out in the UptoDate and Scielo databases using the keywords: “Systemic Lupus Erythematosus”, “Lupus-nephritis”, “Antiphospholipid syndrome”, “Transverse-myelitis”, articles that comprised this association or part of it were selected.

CASE REPORT

Female patient, 22 years old, white, housewife. She had no addictions. In her health history, she has had two pregnancies, the first evolving with cesarean section due to post-natalism (living son, currently seven years old), later in 2022 her second pregnancy evolved with spontaneous abortion in the first trimester (G2C1A1). In 2022, she had multiple episodes of bleeding, requiring several hospitalizations, receiving the diagnosis of Idiopathic Thrombocytopenic Purpura (ITP), and undergoing splenectomy in the same year. Also in 2022, she needed to perform a salpingectomy and right oophorectomy due to ovarian torsion. In addition, she had two episodes of deep vein thrombosis (DVT). Referred to the Emergency Room of Hospital Santa Casa de Maringá in January 2024, from the Emergency Care Unit (UPA), to be evaluated by the Nephrology team, due to the presence of acute renal dysfunction, associated with urinary retention requiring relief bladder catheterization. She brought with her some laboratory tests (Table 1). She reported that in October 2023 she began to experience bilateral loss of strength in her lower limbs, associated with the appearance of purpura on her limbs and trunk. Fifteen days after the current presentation, she began to feel unwell associated with loss of strength in her lower limbs and dyspnea, with an exacerbation of the complaints for 3 days. She also reported visual symptoms, such as bilateral blurring.

At the time of admission, she was hypertensive, with a blood pressure of 213 x 164 mmHg (without a previous diagnosis of systemic arterial hypertension). She denied alopecia, weight loss, and oral and genital ulcers. At the time, he was not taking any continuous medications. Laboratory tests were requested upon admission (Table 1) and an ultrasound of the kidneys and urinary tract (Images 1 and 2), and hospital admission was chosen to complement the diagnostic investigations.

Laboratory tests revealed anemia with schistocytes and thrombocytopenia. In addition, he had significant renal dysfunction (creatinine 4.3 and GFR 14 ml/min/1.73). A chest X-ray was performed, which showed evidence of cardiomegaly (Image 3); Serology

results for HIV, Hepatitis B, and C were all negative. VDRL (1:2) was present. Due to a hypertensive tendency in the following days, Amlodipine 5 mg/day and Methyldopa 500 mg (12/12) were started.

It was decided to empirically start pulse therapy with Methylprednisolone 1,000 mg for 3 days (01/10/24 - 01/13/24), associated with Albendazole 400 mg for 5 days for prophylaxis of parasites while awaiting the other laboratory results.

In the following days, laboratory confirmation of Systemic Lupus Erythematosus was performed, noted by the presence of reactive Antinuclear Factor (ANA) with a titer of 1:640, with a fine speckled nuclear pattern. Presence of fractions of the complement system, serum C3 and C4, consumed, reactive anti-native DNA autoantibodies, with a titer of 1:40 and strongly positive anti-SM autoantibodies (Table 1). The patient was evaluated by the rheumatology team, which suggested starting therapy with Hydroxychloroquine 400 mg/day; Subsequently, results for anti-beta 2-glycoprotein IgM and anticardiolipin IgM antibodies were obtained, with highly positive titers.

On the eighth day of hospitalization, renal replacement therapy was chosen due to uremia resistant to clinical measures. The patient continued to complain of reduced strength in her lower limbs. She was evaluated by the neurology team, who noted the presence of symmetrical paraparesis of the lower limbs, associated with signs of pyramidal release (exacerbation of patellar reflexes, patellar and calcaneal clonus, and bilateral crossed extensor reflex). No sensory involvement was noted. Therefore, a neuraxial magnetic resonance imaging (MRI) was performed, which identified signs of extensive longitudinal myelitis in the cervical and dorsal spinal cord, extending cranially to the medulla (images 4 and 5).

After bureaucratic approval of the treatment regimen proposed by the team (Euro-Lupus Trial), the infusion of Cyclophosphamide was started. This regimen consists of the administration of 500 mg (i.v.) every two weeks for three months (total dose of 3 g), followed by maintenance with Azathioprine. Subsequently, the result of a renal biopsy performed at this service was obtained, which identified lupus nephritis, class IV, and thrombotic microangiopathy in the acute phase. It was decided to start anticoagulation with warfarin.

After the necessary therapeutic adjustments, the patient was discharged from the hospital and referred for outpatient follow-up with the Rheumatology, Nephrology, and Neurology teams, as well as physiotherapy activities for motor rehabilitation. The patient was discharged from the hospital using Hydroxychloroquine 400 mg/day, Prednisone 70 mg/day, Amlodipine 5 mg/day, and Methyldopa 500 mg (12/12). In addition, it was

necessary to remain on chronic hemodialysis in our service, due to non-recovery of renal function.

After approximately 20 days of hospital discharge, the patient presented a decrease in anti-DNA (1:40□1:10), in addition to showing improvement in C4 (5□9.1). The patient evolved with slow but progressive improvement of the paraparesis of the lower limbs. Previously, she had difficulty standing up alone but currently walks alone without assistance.

IMAGING EXAMS

Image 1: Topical kidneys, preserved contours, and dimensions. Good cortical-sinus differentiation.

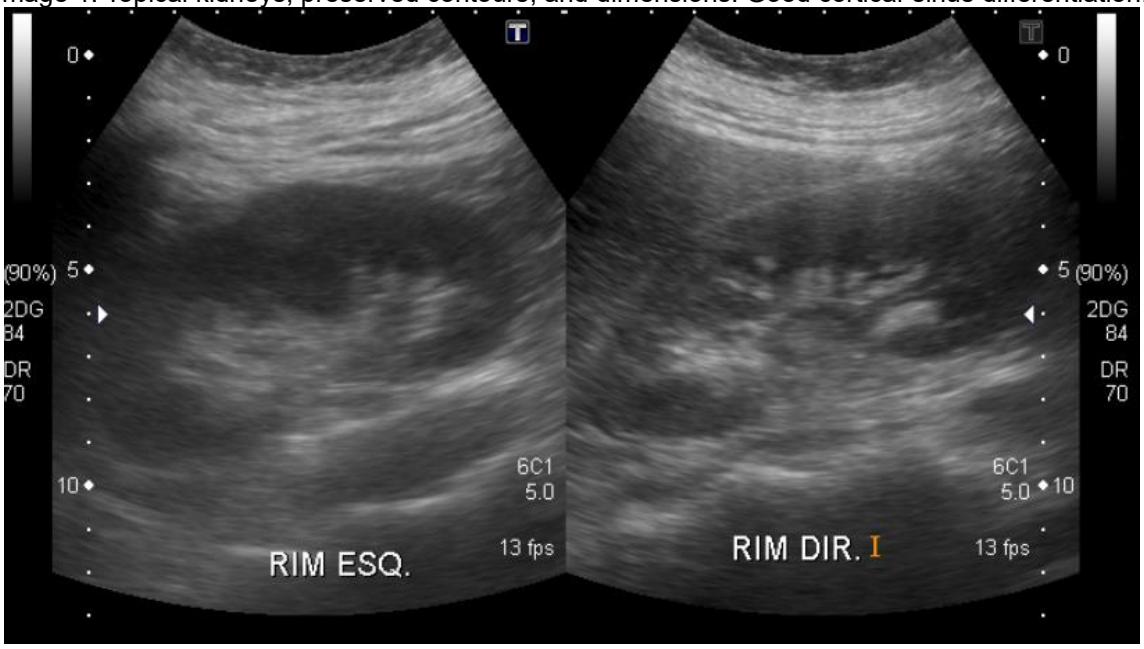


Image 2: Discrete perirenal fluid layer on the right.

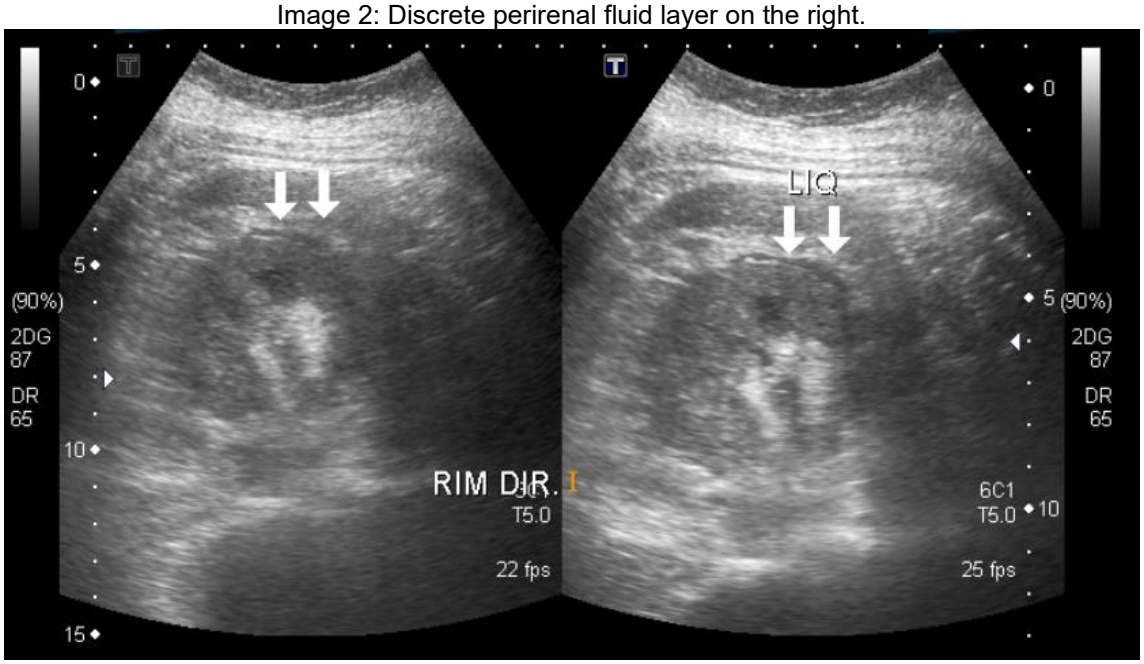


Image 3: Lungs with preserved transparency and vascular design and increased cardiothoracic index

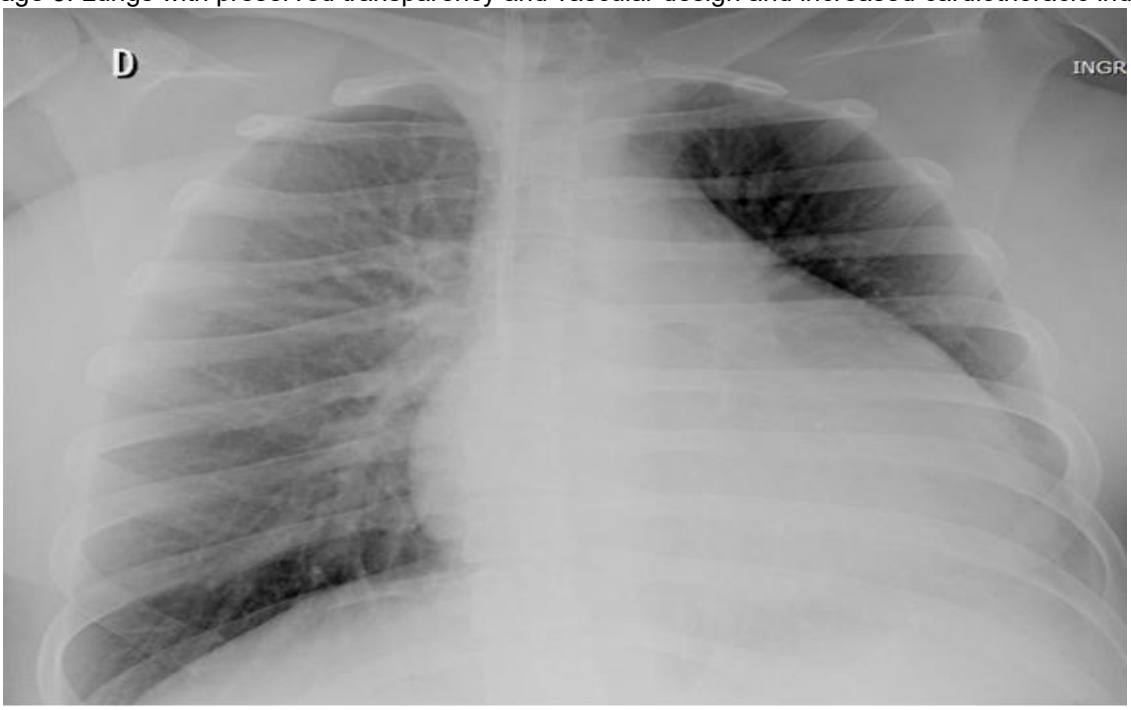


Image 4: Signs of longitudinally extensive myelitis in the cervical and dorsal spinal cord, extending cranially to the medulla oblongata.

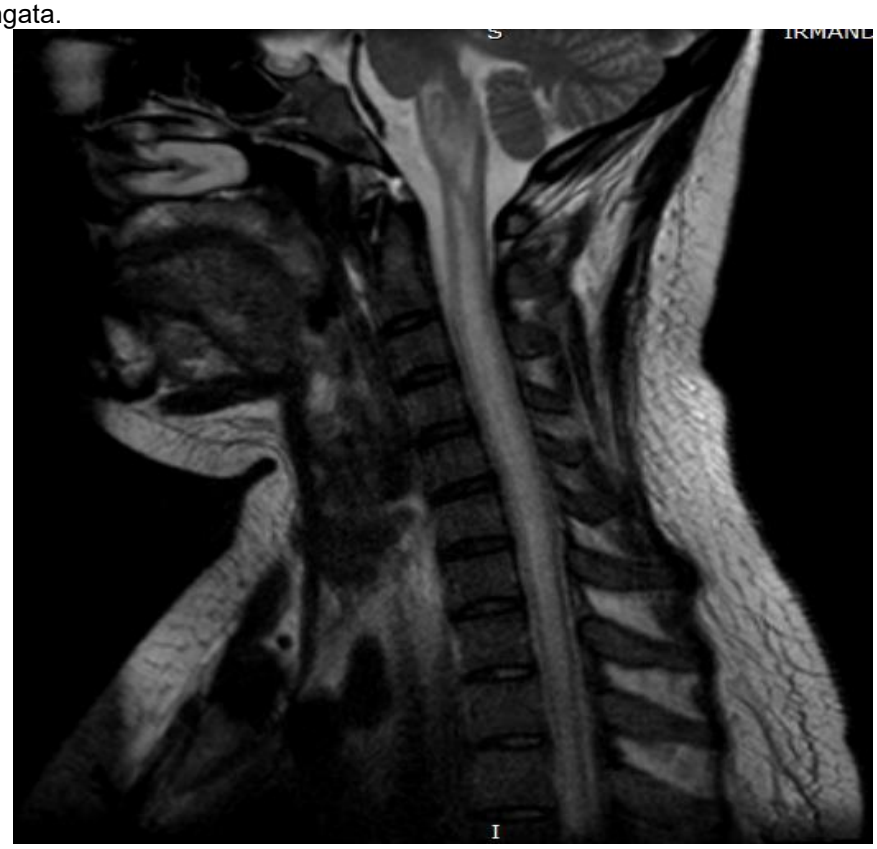
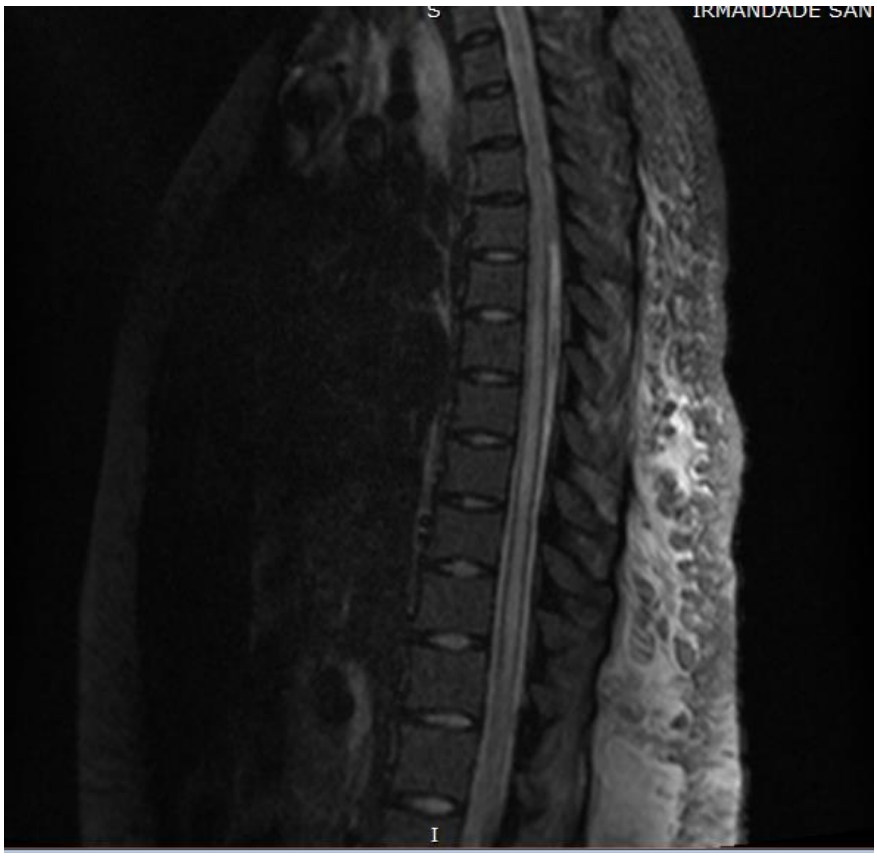


Image 5: Longitudinal extensive spinal cord injury with hyperintense signal on T2/STIR, with centromedullary predominance.



LABORATORY TESTS

Table 1 - Laboratory Tests Performed During Hospitalization and Outpatient Follow-up

TESTS	REF. RANGE	01/06/2024	01/08/2024	01/13/2024
Hb	12-16	8.4	8.2*	
Ht	36-46 %		26.6	
MCH				
Reticulocytes	0.5-2%		3.5%	
LDH	125-220		655	
Direct Coombs	NEGATIVE		NEGATIVE	
Leukocytes	5,000-10,000		14,010 (b 1%)	
Platelets		39,000	58,000	
Urea	15-40	97	122	
Creatinine	0.5-1.1	3.5	4.3	
CRP	<1		0.79	
Sodium (Na)			140.8	

TESTS	REF. RANGE	01/06/2024	01/08/2024	01/13/2024
Potassium (K)			4.7	
Bicarbonate			16.1	
ESR				
Urinalysis		Ptn ++	Ptn + Hb +++ Leuk > 2 million; granular casts	
24h Proteinuria	<300			4,923 mg/24h
HIV 1 and 2	NON-REACTIVE		NON-REACTIVE	
HCV	NON-REACTIVE		NON-REACTIVE	
HBsAg	NON-REACTIVE		NON-REACTIVE	
VDRL			REACTIVE (1:2)	
C3	90-170		38	
C4	12-36		5	
INR			1.06	
Total Bilirubin	0.2-1.2		BT 0.46 / BD: 0.20 / BI: 0.26	
Lupus Anticoagulant	NOT DETECTED		DETECTED (1:26)	
Anti-DNA Antibody	NON-REACTIVE		REACTIVE (1:40)	
ANA (Antinuclear Factor)	NON-REACTIVE		1:640 (Speckled pattern)	
Lupus Anticardiolipin	NON-REACTIVE		IgM REACTIVE / IgG NON-REACTIVE	
Anti-Beta 2 Glycoprotein 1	NON-REACTIVE		IgM and IgG REACTIVE	
Anti-RO Antibody	NON-REACTIVE		REACTIVE	
Anti-LA Antibody	NON-REACTIVE		REACTIVE	
Anti-SM	NON-REACTIVE		REACTIVE	
Anti-RNP	NON-REACTIVE		REACTIVE	
Protein Electrophoresis			MONOCLONAL PEAK ABSENT	

TESTS	REF. RANGE	01/06/2024	01/08/2024	01/13/2024
Presence of schistocytes and elliptocytes				

Table 2 - EULAR/ACR 2019 Criteria: Entry Criterion + Additional Criteria ≥ 10 Points, with at Least One Clinical Criterion

CRITERIA	PATIENT	POINTS
3.3 ENTRY CRITERION		
ANA > 1:80	REACTIVE 1:640	OK
3.4 ADDITIONAL CRITERIA		
FEVER	NO	0
HEMATOLOGICAL	THROMBOCYTOPENIA	+4
NEUROPSYCHIATRIC	MYELOPATHY	0
MUCOCUTANEOUS	ALOPECIA	+2
SEROSITIS	NO	0
MUSCULOSKELETAL	NO	0
RENAL	LUPUS NEPHRITIS CLASS IV	+4
3.5 LABORATORY CRITERIA		
ANTIPHOSPHOLIPID ANTIBODIES	POSITIVE	+3
COMPLEMENT	C3 = 38 / C4 = 5	+4
SPECIFIC ANTIBODIES	ANTI-DNA 1:40 / ANTI-SM >330	+6
TOTAL SCORE		+23

DISCUSSION

The case presents a young female patient, who has common epidemiological characteristics in patients diagnosed with autoimmune diseases, such as Systemic Lupus Erythematosus. During further investigation, a speckled nuclear FAN of 1:640 was revealed, anti-native DNA 1/40, anti-Ro (>240) and Anti-Smith (>330) were strongly positive. From this, it was possible to conclude the diagnosis of SLE, according to the diagnostic criteria of the European League Against Rheumatism / American College of Rheumatology (EULAR / ACR) of 2019, which recommends as an entry criterion a FAN ≥ 1:80 added to additive criteria of ≥ 10 points (comprising domains such as constitutional, cutaneous, articular, neurological, hematological, renal, antiphospholipid antibodies, complement, serous, highly specific antibodies). The application of the criteria in the patient of the reported case added

23 points (Table 2). Most patients with systemic lupus erythematosus (SLE) will have clinical evidence of kidney disease, usually an abnormal urinalysis, at some point during the disease. Lupus nephritis typically develops early in the course of the disease. Clinically evident kidney disease eventually occurs in up to half of patients with SLE, and up to 10 percent of patients with LN will develop end-stage renal disease. In a cohort of 1,827 patients with newly diagnosed SLE, LN occurred in 700 patients (38%). Kidney disease is typically detected in most patients with systemic lupus erythematosus by an abnormal urinalysis with or without an elevated plasma creatinine concentration. The most common abnormality seen in patients with lupus nephritis is proteinuria. Other common clinical manifestations include microscopic hematuria with or without red blood cell casts, impaired renal function, nephrotic-range proteinuria or nephrotic syndrome, and hypertension 8.

Elevated anti-double-stranded DNA (anti-dsDNA) titers and low complement levels (C3 and C4) usually indicate active SLE, particularly LN. The diagnosis of LN is ideally confirmed by renal biopsy.

The pattern of glomerular injury seen in SLE is usually related to the site of formation of immune deposits, which are primarily due to anti-double-stranded DNA. However, immune complexes may also include chromatin, C1q, laminin, Sm, La (SS-B), Ro (SS-A), ubiquitin, ribosomes, and glomerular elements, including parts of the glomerular basement membrane (GBM), and mesangium. Immune deposits in the LN may occur in the mesangial, subendothelial, and/or subepithelial compartments of the glomerulus 9.

In the patient's case, the condition presented with a reduction in the glomerular filtration rate (by CKD-EPI: 18 ml/min/ 1.73), oliguria, and proteinuria at nephrotic levels (24-hour proteinuria 4,923 mg). When performing the renal biopsy, she was classified by the lupus nephritis classification system as diffuse proliferative form, class IV, where more than 50 percent of the glomeruli are affected. In addition, thrombotic microangiopathy was identified in the acute phase, with an activity index of 8 and chronicity of 3, 25% fibrosis of the interstitium, and diffuse inflammatory infiltrate, intact basement membrane, arteriole with fibrinoid necrosis and concentric neointimal proliferation in onion skin (histopathological characteristics of thrombotic microangiopathy).

Renal biopsy is important to define the nature of renal involvement, exclude other causes of renal injury, and determine the histopathological subtype of LN. Biopsies are also important to assess the activity and chronicity of the disease 10.

Determining the nature and class of LN is important for the following reasons: treatment is guided by the histological subtype, degree of activity, and chronicity, and by complicated lesions, such as interstitial nephritis and thrombotic microangiopathy.

A biopsy can also identify entities other than LN. Some patients with SLE and nephrotic proteinuria will have lupus podocytopathy, without major deposition of immune complexes, but with effaced podocyte processes, as seen in minimal change disease. Others with renal disease may have thrombotic microangiopathy or predominant tubulointerstitial involvement, rather than significant glomerular involvement. In addition, it is important to perform a biopsy, since the clinical presentation may not accurately reflect the severity of the histological findings 10.

The patient in question presented anemia with microangiopathic hemolytic features, confirmed by the presence of schistocytes, thrombocytopenia, and elevated lactate dehydrogenase (LDH), raising clinical questions about the possibility of thrombotic microangiopathy associated with SLE. This can be confirmed with positivity for antiphospholipid antibodies and renal biopsy.

Among several renal vascular alterations in lupus, thrombotic microangiopathy is among the most serious and with high mortality. 11. In fact, TMA in lupus nephritis can arise in a group of diseases, including antiphospholipid syndrome (APS), thrombotic thrombocytopenic purpura, hemolytic uremic syndrome (HUS), and scleroderma.

Renal involvement can be a serious problem for patients with antiphospholipid syndrome (APS). Clinical and laboratory features of renal involvement in APS include systemic arterial hypertension, hematuria, and progressive acute and chronic renal failure with low-level proteinuria that may progress to nephrotic proteinuria. The antiphospholipid antibodies typically tested in routine laboratory practice are IgG and IgM anticardiolipin antibodies. The presence of IgG and IgM anti-β2 glycoprotein-I (aβ2GPI) antibodies, also detected by ELISA, should also be evaluated 12.

One of the best-known and most important renal features of APS nephropathy is thrombotic microangiopathy. An acute lesion has been reported to be present in up to 20% of patients with primary APS undergoing renal biopsy. Histopathologically, TMA is characterized by the absence of inflammatory cells and vascular immune deposits, and by the presence of fibrin thrombi in the glomeruli and throughout the intrarenal vascular circulation 13.

Although SLE is associated with an increased risk of arterial and venous thromboembolic events independent of aPL, results from observational studies suggest that this risk may be further increased in the presence of aPL. A review of observational studies estimated an annual risk of thrombosis among individuals positive for aPL, including those with systemic rheumatic disease, of 5.3 percent; the annual risk among individuals positive for APL, without systemic rheumatic disease, was estimated at <1 percent 14.

Our patient's clinical presentation began with bilateral loss of strength in the lower limbs, and extensive longitudinal myelitis was confirmed using magnetic resonance imaging of the entire neuroaxis. Myelopathy is a rare manifestation of the central nervous system in SLE and affects 1 to 2% of patients 15. In 1999, the American College of Rheumatology established the criteria for neuropsychiatric manifestations in SLE, including myelopathy. This should be considered if the patient presents rapid progression (hours or days) of one or more signs/symptoms: bilateral muscle weakness in the lower limbs, with or without the involvement of the upper limbs; sensory disorder, with a similar level of motor involvement, with or without intestinal or bladder involvement. An expansive lesion that causes spinal cord compression should be ruled out, as well as a lesion in the cauda equina 16.

Myelopathy may present as transverse myelopathy with sectional involvement of one level of the spinal cord or as longitudinal myelopathy, in which more than three segments are affected, continuously or not 17. The cause of myelopathy in SLE is not well understood and both the participation of thrombosis and vasculitis have been implicated in this process.

Some authors suggest that there is a relationship between antiphospholipid antibodies and myelopathy, which would reinforce the hypothesis of thrombosis, but other studies do not confirm this association 18. The findings of the analysis of cerebrospinal fluid (CSF) are nonspecific. Some authors have found increased cellularity and protein levels, but CSF is often normal in patients with myelopathy 19. In the case reported, CSF collection was not performed, since MRI had already clearly demonstrated the presence of myelitis.

Magnetic resonance imaging is the most sensitive imaging test for evaluating spinal cord injury, including cases of myelopathy associated with SLE. The MRI imaging protocol should cover the level corresponding to the neurological damage observed on clinical examination, but it is recommended that the entire spinal cord be studied. Imaging findings may vary, including hyperintense signals on T2-weighted images of the spinal cord, swelling in cases of spinal cord edema, and contrast uptake. Among these, the most frequent finding is signal alteration, as was also observed in our report 20.

A study by Birnbaum et al. compared patients with spinal cord injuries in the white matter (spasticity and hyperreflexia) with those with injuries in the gray matter (flaccidity and hyporeflexia) and concluded that injuries in the gray matter are related to irreversible paraplegia and greater disease activity 21.

Treatment of myelopathy should be instituted immediately after diagnosis, since this manifestation has a reserved prognosis, with high morbidity in up to 50% of cases and high mortality. The delay in starting adequate treatment was the factor for unfavorable outcomes

highlighted by all authors. The combination of intravenous methylprednisolone and cyclophosphamide pulses is the treatment considered standard for these patients 22.

CONCLUSION

From the above, it is possible to conclude the importance of rapid detection of SLE, especially considering the triple involvement presented by our patient, which, although rare, when present demonstrates great morbidity. It is understood that the prompt establishment of the correct treatment can change the entire trajectory of the affected individual.

Therefore, to assist and alert other health professionals, this case is described, as well as all the investigation and management approached by our team...

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