

## ANCA-Positive pauci-immune crescentic glomerulonephritis in a patient with systemic lupus erythematosus

Glomerulonefrite rapidamente progressiva ANCA-Positiva pauci-immune em paciente com lúpus eritematoso sistêmico

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### ABSTRACT

The pauci-immune crescentic glomerulonephritis (PICGN) is generally associated with small-vessel vasculitis with a few reported cases associated with other autoimmune diseases such as Systemic Lupus Erythematosus (SLE). We present the case of a female 34-year-old patient with acute kidney injury symptoms with indication for renal replacement therapy in the context of clinical SLE diagnosis. A kidney biopsy was conducted and it was found that most glomeruli showed some segmental sclerosis with synechia to the Bowman's capsule. 67% of the glomeruli had fibroepithelial crescents. Moreover, the interstitial space had a moderate lymphomononuclear infiltration and mild fibrosis. In the arterioles, there were walls thickened by subintimal sclerosis. Direct immunofluorescence detected limited IgM and C3 deposits in capillary loops and negative mesangium for IgG, IgA and C1q. A therapy using corticosteroids and intravenous cyclophosphamide was initiated with stable evolution. PICGN associated with SLE is a rare pathology with clinical presentation, varied evolution and without a standard medical treatment.

**Keywords:** anti-neutrophil cytoplasmic antibody-associated vasculitis; glomerulonephritis; lupus erythematosus, systemic.

### RESUMO

A glomerulonefrite rapidamente progressiva pauci-immune apresenta-se geralmente associada a vasculite de pequenos vasos, com poucos casos associados a outras doenças imunes como o lúpus eritematoso sistêmico (LES). Apresentamos no presente artigo o caso de uma mulher de 34 anos de idade com sintomas de insuficiência renal aguda e indicação de terapia renal substitutiva, no contexto de diagnóstico clínico de LES. A biópsia renal realizada revelou que a maioria dos glomérulos apresentavam um certo grau de esclerose segmentar e sinéquias com a cápsula de Bowman. Sessenta e sete por cento dos glomérulos apresentava crescentes fibroepiteliais. Além disso, o espaço intersticial exibia infiltrado linfomononuclear moderado e fibrose discreta. Nas arteríolas, as paredes encontravam-se espessadas por esclerose subintimal. A imunofluorescência direta detectou depósitos limitados de IgM e C3 nas alças capilares e mesângio negativo para IgG, IgA e C1q. Tratamento com corticosteroides e ciclofosfamida endovenosa foi iniciado com evolução estável. A glomerulonefrite rapidamente progressiva pauci-immune associada a LES é uma patologia rara com manifestação clínica e evolução variada, sem tratamento clínico padronizado.

**Palavras-chave:** glomerulonefrite; lúpus eritematoso sistêmico; vasculite associada a anticorpo anticitoplasma de neutrófilos.

### INTRODUCTION

The rapidly progressive glomerulonephritis (RPGN) is a syndrome characterized by a sudden loss of kidney function associated with the presence of more than 50% of glomeruli with epithelial crescents in the kidney biopsy.<sup>1-4</sup> The pauci-immune crescentic glomerulonephritis (PICGN) is the

most common RPGN, representing more than 80% of the cases and it is defined as the extensive glomerular inflammation with few or no immune deposits, generally associated with ANCA-associated vasculitis.<sup>1-6</sup> However, the frequency of the RPGN causes will depend on the type of population included in the study.<sup>7</sup> In

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this regard, according to a study conducted in our environment with a sample composed mainly of young women, the most common causes were first, SLE (44.4%) and second, vasculitis (37%).<sup>8</sup>

PICGN-associated vasculitides are small-vessel vasculitides and include granulomatosis with polyangiitis, microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis or kidney vasculitis.<sup>1,2</sup> Around 90% of patients with PICGN have circulating anti-neutrophil cytoplasmic antibodies, which results in the nomenclature of ANCA-associated vasculitis (AAV).<sup>1,2</sup>

PICGN is rarely observed during the course of other immunological diseases as in the mixed connective tissue disease (MCTD) or SLE.<sup>9</sup> This last association has few cases reported in the medical literature.<sup>9-17</sup>

We present a case of a patient with systemic lupus erythematosus and ANCA-positive pauci-immune crescentic glomerulonephritis.

## CASE REPORT

A 34-year old female from Lima, Peru presented a 19-year history of pulmonary tuberculosis and had a niece with a diagnosis of chronic kidney disease on hemodialysis due to bilateral renal hypoplasia. The attending patient had been experiencing a month before the evaluation, a clinical condition characterized by distal edema and general weakness.

A week before she was admitted, the edema was generalized, and dyspnea on light exertion, blurred vision, oliguria, nausea and vomiting occurred. The physical exam showed a high blood pressure, anasarca and mucocutaneous pallor. The patient was admitted through the emergency department with symptoms of acute kidney injury (serum creatinine of 9.26 mg/dL) complicated by fluid overload, uremic gastropathy and severe hyperkalemia. A dialytic support with conventional hemodialysis was initiated.

Positive antinuclear antibody (ANA), low complement, positive direct Coombs, Anti MPO ANCA-positive and non-nephrotic-range proteinuria were found within the abnormal ancillary exams (Table 1). The renal ultrasound showed kidneys of normal size and parenchyma.

A kidney biopsy was conducted 20 days after she was admitted to the hospital and 2 days after 3 methylprednisolone pulses were completed. Biopsy showed 11 glomeruli, 2 of which were globally sclerosed. Most viable glomeruli had some segmental sclerosis

(1+ to 3+) with synechia to Bowman's capsule and 7 (64%) had fibroepithelial crescents. There was a moderate tubular atrophy, as well as tubules with regenerating epithelium. Moreover, the interstitial space had a moderate lymphomononuclear infiltration and mild fibrosis. In arterioles, there were walls thickened by subintimal sclerosis (Figures 1 and 2). The direct immunofluorescence detected limited IgM and C3 deposits in capillary loops and negative mesangium for IgG, IgA and C1q.

The patient received intravenous methylprednisolone (1000 mg daily) during 3 days along with intravenous cyclophosphamide (500 mg), followed by oral prednisone and enalapril. When the patient was discharged, she continued the hemodialysis program with partial improvement in the kidney function, almost 30 days after starting immunosuppression but without clinical conditions to suspend dialysis. The second dose of cyclophosphamide was scheduled.

## DISCUSSION

PICGN is the most common cause of RPGN and is commonly observed in the ANCA-associated vasculitis.<sup>1,4</sup> In patients with SLE, RPGN cases usually corresponds to Type II.<sup>3,4</sup> Although it is possible to find a positive ANCA result in up to 20% of patients with SLE without being vasculitis,<sup>17</sup> overlap cases between SLE and vasculitis are known.<sup>18,19</sup> However, the association between PICGN and SLE is only known due to reported cases.<sup>9-17</sup>

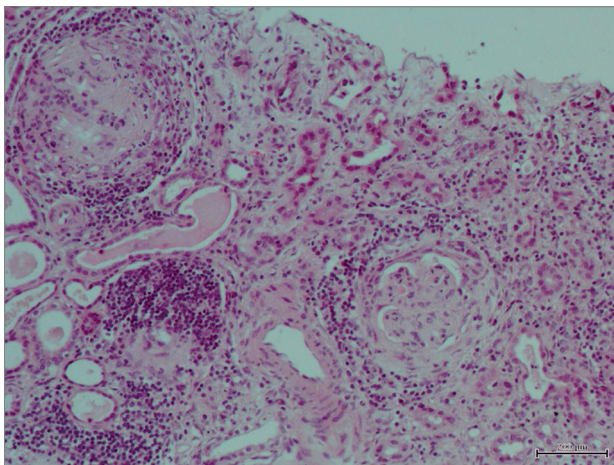
PICGN cases associated with other connective tissue diseases are very rare. Therefore, this demonstrates indirectly that there are still aspects of the physiopathology of glomerulonephritis crescents to be learnt. The first studies about RPGN identified a mixture of immunological components in epithelial crescents varying according to the phase and severity of the disease.<sup>3</sup>

For PICGN, despite the absence of immune deposits, pathogenic mechanisms in ANCA-associated vasculitis are mediated by the development of immune autoantibodies.<sup>2</sup> However, although there is a lot of *in vitro* evidence that explain the role of MPO-ANCA, we do not have convincing animal models for PR3 ANCA.<sup>3</sup> On the other hand, other antibodies different from ANCA have been identified in cases of pauci immune glomerulonephritis such as in the case of protein 2 antibodies of the lysosomal membrane (LAMP-2).<sup>3</sup> In fact, some PICGN cases reported in

**TABLE 1** EVOLUTION OF LABORATORY TESTS OF THE CASE REPORT

TESTS PERFORMED	Day 2	Day 13	Day 15
Urea (mg/dL)	174.3	244	83.5
Creatinine (mg/dL)	9.26	17	5.9
Hemoglobin (g/dl)	6.7	5.6	6.6
pH	7.28	7.30	7.35
HCO <sub>3</sub> (mMol/L)	13.2	13	20
Potassium (mEq/L)	5.7	6.5	3.8
24-hour proteinuria (gr)	2.6	2.5	1.1
Complete urinalysis	Leukocytes 15xC, RBCs 47xC, Proteins ++, blood ++		
ANA	1/160		
MPO ANCA (< 20 U/ml)	132.7		
C3 (Normal range: 90-180 mg/dL)	81		
Direct Coombs	Positive ++		

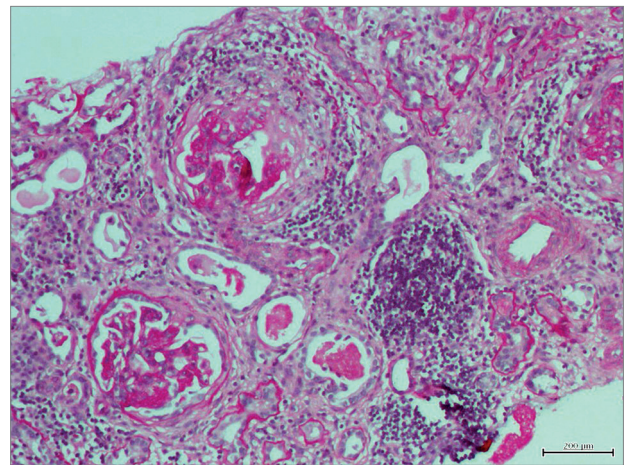
**Figure 1.** Two glomeruli are observed. The left one shows moderate sclerosis and fibroepithelial crescent. The right one has segmental sclerosis; both are surrounded by lymphomononuclear cells. Moderate tubular atrophy. Interstitial space with moderate infiltration of lymphomononuclear cells (H\_E 20x).



patients with SLE show negative ANCA, which could be due to the activation of these other antibodies.<sup>15,20,21</sup>

Clinical presentation of the cases reported in the medical literature are varied. Not all the patients had complete criteria for the SLE diagnosis, which could be due to the fact that they are patients in early stages and that they do not meet the disease criteria.<sup>9</sup> The patient in our case met the SLICC criteria for Systemic Lupus Erythematosus (4 criteria: kidney involvement, positive ANA, positive direct Coombs and low complement) and presented an SLE disease activity score (26 points according to SLEDAI). When obtaining the results of the kidney biopsy suggesting vasculitis,

**Figure 2.** Glomerulus located at the upper part shows segmental sclerosis and fibroepithelial crescent, while the one located at the lower part has segmental sclerosis and synechia to the Bowman's capsule. Interstitial space with lymphomononuclear infiltration (PAS-20x).



the Birmingham's vasculitis activity score was applied with severe results (15 points), whereby the immunosuppressive treatment began.

There is no standardized protocol for PICGN cases, and the regimens used in the reported cases are similar to those used for cases of proliferative lupus nephritis with dissimilar results.<sup>9-17</sup> Although there are alternatives for RPGN cases, studies show methodological biases; therefore, the conclusions cannot be definitive.<sup>22</sup> Likewise, in view of the possible use of plasmapheresis as an alternative in case of a severe vasculitis, some authors have suggested that more studies are necessary to clarify the potential role of this therapy in cases of vasculitis.<sup>23</sup>

In conclusion, it is rare that a patient with SLE diagnosis shows PICGN. There is no standard treatment, but it is common the use of the combination between cyclophosphamide and corticosteroids with variable evolution.

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