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CASE REPORT

Complement 3 Glomerulonephritis is an Overlap Lupus-Sjögren Syndrome: A Case Report

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Abstract

We herein report a case of a 47-year-old male, with symptoms of thoracic pain and recent history of evanescent malar rash, diffuse migratory polyarthralgia, oral and ocular dryness. Laboratory results showed acute kidney injury and positivity for anti-nuclear, anti-DNA, anti-Ro and anti-LA antibodies. Study led to diagnosis of overlap systemic lupus erythematosus (SLE) and Sjögren's syndrome (SS). Results of kidney biopsy presented an exclusivity of C3 in immunofluorescence, consistent with histopathological diagnosis of Complement 3 glomerulopathy. Renal involvement of SLE classically involves an immune complex-mediated glomerulonephritis which is known to activate classical pathway of complement. On the other hand, C3 glomerulopathy is a rare kidney disease characterized by dysregulation of the alternative pathway of the complement system. Previous described cases that correlated C3 glomerulopathy and autoimmune disease presented genetic alterations. The genetic study of our patient, however, did not identify any pathogenic genetic variables in complement genes. We provide a review of current evidence in the search for other the pathophysiological mechanisms that may provide an answer as to why this case happened. To our knowledge this is the first described case of overlap SLE-SS with histological findings of C3 glomerulopathy. All authors declare they have no conflict of interest.

Keywords: Complement 3 glomerulopathy, Systemic Lupus Erythematosus, Sjögren's Syndrome

1. Introduction

Renal involvement in systemic lupus erythematosus (SLE) classically involves an immune complex-mediated glomerulonephritis which is known to activate classical pathway of complement(1). Lupus nephritis is characterized by immunoglobulin and complement deposits within the glomeruli, tubular basement membranes and vessel walls. Immunofluorescence glomerular deposits stain dominantly for IgG with co-deposits of IgA, IgM, C3 and C1q in the so-called full house pattern.

The term C3 glomerulopathy (C3G) was adopted by expert consensus in 2013 to define a group of kidney diseases driven by dysregulation of the complement cascade(2). C3G diagnosis is made through histopathology with g lomerular immunofluorescence staining exclusive or predominant for C3(3).

The present case reports a patient with a diagnosis of SLE according to ACR/EULAR 2019 criteria (4), with exclusive findings of C3G in renal biopsy. The patient's treatment, follow-up and outcome are presented.

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2. Case Report

We present the case of a 47-year-old male from Rumania. History of renal function was normal. There was a lack of nephropathy and autoimmunity disease in family history.

He had previous medical history of hypertension. An active smoker,he was receiving pneumology follow-up since 2014 for findings of pulmonary emphysema and small multiple calcified mediastinal adenopathies. A year before current hospitalization, he presented an episode of non-ST-segment elevation myocardial infarction (NSTEMI) with a non-significant lesion in anterior descending artery without pathological findings in echocardiography. During that time, he presented hair and 10 kg weight loss added to episodes of evanescent malar rash that appeared during more stressful periods and diffuse migratory polyarthralgia, as well as oral and ocular dryness.

The patient presented to the emergency complaining of 5-hour-long atypical thoracic pain and dyspnea, which worsened with breathing and movement. Electrocardiogram (ECG) reading was compatible with pericarditis, echocardiography showed normal ventricular function and no signs of endocarditis or pericardial effusion.

Blood test revealed acute kidney injury (Cr 1.5 mg/dL) alongside hematuria and proteinuria in urinalysis; anemia with positive coombs test without signs of thrombotic microangiopathy on peripheral blood smear.

Autoimmunity analysis showed positivity for ANA and anti-DNA antibodies as well as for anti-Ro and anti-LA antibodies. Serum complement C3 was normal with low C4. Anti-neutrophil cytoplasmatic antibodies (ANCA) as well as anti-glomerular basement membrane (Anti-MBG) antibodies were negative. Serological studies for infectious pericarditis agents were run, whose results were negative. The sum of patient's symptomswas consistent with diagnosis of SLE given EULAR 2019 diagnostic criteria, with a SELENA-SLEDAI score of 16.Symptoms of oral and ocular dryness along positivity for Anti-Ro and Anti-La antibodies, led to study with salivary gland scintigraphy confirming Sjögren syndrome (SS). The diagnosis of overlap SLE-SS was made.

Kidney biopsy obtained 33 glomeruli. Segmentary mesangial expansion and diffuse thickening of capillary wall was observed in all glomeruli. 7 glomeruli presented crescents. There was no presence of amyloid material or tubular casts. Immunofluorescence was exclusive for high intensity granular global and diffuse staining of C3 (+++/+++) on glomerular capillaries, images of which, unfortunately, could not be captured. We presentan immunohistochemistry image which also revealed exclusive mesangial positivity for C3d (figure 1). There was no material available for electronic microscopy.

Agenetic-molecular study of the patients complement system was performed. Biochemical and immunological study of complement observed diminished levels of C4, factor B and increased levels of Factor H and serum membrane attack complex (SMAC). Genetic study of complement did not identify any pathogenic genetic variables in complement genes. Factor H autoantibodies and C3Nef determination were negative.

Treatment consisted in corticosteroid pulses followed by oral tappering and iv cyclophosphamide every two weeks for 6 dosages, followingEurolupusNephritis trial guidelines.

Hidroxyclorohine and mycophenolic acid were used for maintenance therapy. A year after hospitalization renal function is normal andproteinuria has decreased to less than 500mg/g with inactive sediment.

3. Discussion

This case report describes a 47-year-old male with previous history of hair loss, polyarthralgia and evanescent malar rash. He presented to the emergency complaining of atypical chest pain and toxic syndrome. Blood test revealed acute kidney injury with positive high-title determination for anti-DNA, ANA, Ro and La antibodies, with normal complement levels.

According to ACR/EULAR 2019 criteria, the patient's symptoms and laboratory findings met the diagnostic criteria for systemic lupus erythematosus (SLE). Further studies, along with the detection of positivity for Anti-Ro and anti-La antibodies, lead to the diagnosis of overlap with Sjögren's Syndrome (SLE-SS).

The occurrence of SLE-SS ranges between 6.5% and 23.2%, and has been reported to occur predominantly in older and female patients (5-7). SLE-SS patients often present a higher presence of neuropathy, and nephropathy is less common compared to SLE patients alone. Anti-Sm and anti-cardiolipin antibodies are also less prevalent in SLE-SS (7). Systemic inflammation -measured by cytokine levels- has been observed to be higher in patients with SLE-SS. There's no reported difference in SLEDAI score between SLE and SLE-SS groups. However, Systemic

Lupus Activity Measure (SLAM) measurements – which grade symptom severity and include subjective symptoms- were reported to be higher in the SLE-SS groups (7).

Renal biopsy findings of our patient showed diffuse and segmentary mesangial hypercellularity, immunofluorescence was exclusive for high intensity C3 (+++/++++) on capillaries. Genetic study of complement was normal except from observed reduced C4 levels, which underlies an alteration of complement through classical pathway.

C3 glomerulopathy (C3G) is defined by the presence of C3 in glomerular immunofluorescence of at least two orders of magnitude at greater intensity than for any other immune reactant. This finding is the single diagnostic criterion (8). Findings on light microscopy are diverse, and range from no glomerular hypercellularity to mesangial proliferative, endocapillary proliferative, exudative, membranoproliferative, crescentic and sclerosing patterns. The pathology of the disease is caused by dysregulation of the alternative pathway (AP) of complement, with deposition of complement factors and debris in the glomeruli and ensuing inflammation (2, 9,10).

Several mutations including those in CFH, CFHR, CF1, MCP, C3 and CFB have been identified in patients with C3G (11-17). The loss or gain of function of these genes result in overactivation of the alternative complement pathway (18).

Dense deposit disease (DDD) and C3 glomerulonephritis (C3GN) form the components of C3G. Although both entities are driven similarly by alternative complement dysregulation, which pathophysiological mechanisms underly each disease are still unknown. Due to a reported higher C3Nef activity, DDD dysregulation may occur in late components of the alternative complement pathway due to detection of higher levels of soluble C5b-9(19).

Differential diagnosis between the two entities is often difficult because the distinction between these two diseases is based solely on electron microscopic features, which may not be available at many hospitals. Some clinical differences may help distinguish between the two. It has been seen that DDD patients presented more crescentic glomerulonephritis, lower serum C3 levels, onset at younger age and more prevalence of end-stage renal disease in comparison to C3GN (20).

Our case presents two contradictory scenarios. On one hand the clinical and serological study of overlap SLE-SS and genetic study whose only pathological results consist in reduced C4 levels, which underlies a complement alteration through the classical pathway. On the other hand, the diagnosis of C3 glomerulopathy was made through immunofluorescence.

A case of C3 glomerulopathy in the setting of LES has been recently described. In the mentioned case, a mutation of c.1204c>T; p.His402Tyr variant in the CFH was found(21).

In 2016, Alexander et al. reported on a cohort of 65 patients diagnosed with C3G(22). Results found incidence of autoimmune diseases to be higher in patients with C3G. 10 patients presented antinuclear antibody titer abnormalities, and in 6 patients anti-double-stranded DNA antibodies were detected, one of such patients had a diagnosis of SLE. The patients underwent genetic testing, and all carried risk alleles for C3G, the most common of which was FH His402 (c.1204C, pHis402). Conclusions of the study hypothesized that C3G may be secondary to autoantibodies that directly activate the alternative pathway of C3 or indirectly lead to its dysregulation. In these cases, the only clinical or serological evidence of autoimmunity at the outset may be an abnormal autoantibody panel.

As research in the pathophysiology of C3G continues, a recent large case control-study analyzed whole-genome sequence from 165 membranoproliferative glomerulonephritis (MPGN) cases with 6442 controls to investigate the role of genetic variation in the causation of primary MPGN (23). A genetic explanation as to why the disease takes place has been found incompatible due to several newly found reasons. Firstly, it has been seen that different family members do not share the disease. Secondly, C3Nefis detected in a substantial proportion of patients, even those with rare variants in complement gene (11). Finally, a recognized association of MPGN with other autoimmune diseases does exist, (24,25)including a very substantially increased rate of type 1 diabetes in relatives of patients with dense deposit disease (DDD(26). Results did not find rare genetic variations in MPGN, instead, a strong association with common variation at the HLA locus was found, explaining phenotypic association with established autoimmune diseases.

In conclusion, this case provides further evidence of development of C3G in the setting of an autoimmune disorder with a lack of genetic alterations. As far as we know, this is the first case of overlap SLE-SS induced C3G. This case provides further evidence

that an autoimmune baseline disease may act as a trigger for the disruption of the alternative pathway of complement, with the consequence of the development of C3G.

Patient's consent was granted before the elaboration of this case report.

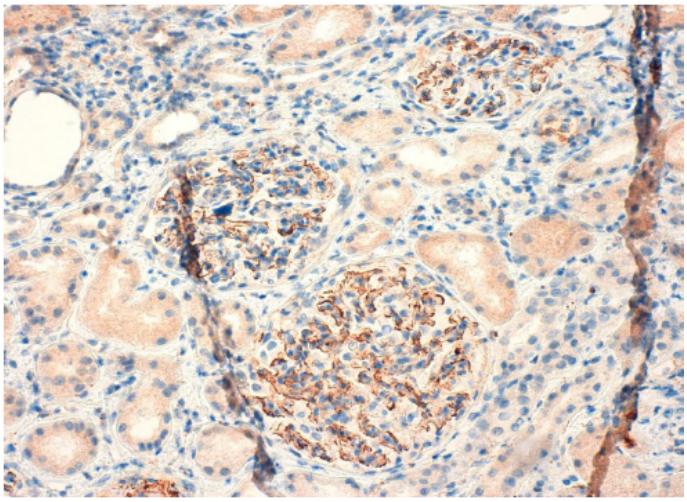

Figure 1. *20x. C3d Immunohistoquemistry of our patient's kidney biopsy, which shows positivity of glomerular staining for C3d.*

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