Case Report

Rare Glomerular Presentation of Essential Cryoglobulinemia without HCV Infection

Dragana Marković¹*, Petar Djurić¹, Aleksandar Janković¹, Ljiljana Bogdanović³, Snežana Pešić¹, Nada Dimkovic⁴, Radomir Naumović¹,²

¹Clinical Department for Nephrology, Zvezdara University Medical Center, Belgrade, Serbia
²Medical Faculty, University of Belgrade, Belgrade, Serbia
³Institute of Pathology, Medical Faculty, University of Belgrade, Serbia
⁴Academy of Medical Sciences of the Serbian Medical Society, Serbia

*Corresponding Author: Dragana Marković, Clinical Department for Nephrology, Zvezdara University Medical Center, Belgrade, Serbia, E-mail: dra.markovic@gmail.com

Received: 15 January 2021; Accepted: 02 February 2021; Published: 10 March 2021

Abstract

Membranoproliferative glomerulonephritis (MPGN) is characterized by mesangial cell proliferation and structural changes in glomerular capillary walls and double-contoured glomerular basement membrane (GBM). Usually, it is connected with cryoglobulinemia which is defined by the presence of a circulating, a cold-precipitating immunoglobulin. The chemical and immunological features of the cryoglobulins are used to define three types of cryoglobulinemia. In this report we describe the third case of MPGN type II with essential cryoglobulinemia without HCV infection, which is usually defined in the literature as MPGN type II. Here, we present 61-years old woman previously diagnosed with MPGN in 2012 at another institution. At that time, she was not examined in terms of cryoglobulinemia. Initially she was treated with pulses of methylprednisolone, then oral corticosteroids until cessation when complete remission was achieved. Meanwhile, she had two relapses of the disease. In October 2020 we re-evaluated her and found out positive cryoglobulins in repeating testing. Serological studies for anti-neutrophil cytoplasmic antibodies (ANCA), myeloperoxidase and proteinase 3, anti-double stranded DNA antibodies, anti-hepatitis C antibodies, anti-HIV antibodies and anti-hepatitis B surface antibodies were all negative. Serum M protein or monoclonal IgM were not detected. Percutaneous renal biopsy was compatible with the diagnosis of...
MPGN. Based on clinical, laboratory and histological evaluation, it was concluded that the patient had a MPGN with essential cryoglobulinemia. Therapy with mycophenolate mofetil had a beneficial effect on the course of disease and the patient achieved partial remission and stable renal function for the last 3 months of follow-up. Since the therapy for MPGN with essential cryoglobulinemia is not standardized, further research in the field is needed.

**Keywords:** Cryoglobulinemia; Membranoproliferative glomerulonephritis

**1. Introduction**

Membranoproliferative glomerulonephritis (MPGN) is an uncommon kidney disorder characterized by mesangial cell proliferation and structural changes in glomerular capillary walls [1] and double-contoured *glomerular basement membrane* (GBM). It is also termed mesangiocapillary GN and it accounts for approximately 7%-10% of all cases of biopsy-proven GN [2]. Traditionally, MPGN has been further classified based on the findings of electron microscopy (EM) as primary MPGN type I (MPGN I), MPGN II, and MPGN III or secondary MPGN [2]. Type I (classic MPGN), the most common variant, is characterized by the presence of subendothelial deposits of immune complexes associated with activation of the classical complement pathway [1]. Type II MPGN (dense deposit disease), is a unique variant characterized by the presence of additional intra-membranous dense deposits [1]. Type III MPGN, which some pathologists consider as a morphologic variant of type I, is characterized by the presence of additional subepithelial deposits [1]. A new classification of MPGN was developed, based on pathophysiology and considering whether immunoglobulins accompany the complement using immunofluorescence staining on biopsy specimens [3].

Cryoglobulinemia is defined by the presence of a circulating, a cold-precipitating immunoglobulin [4]. The chemical and immunological features of the cryoglobulins are used to define three types of cryoglobulinemia. Type I cryoglobulinemia or simple cryoglobulinemia is characterized by a single monoclonal Ig, which is usually an IgM or IgG. In type II cryoglobulinemia, polyclonal immunoglobulins form immune complexes with one or more monoclonal immunoglobulins. The most common form combines a monoclonal IgM and polyclonal IgG (mixed monoclonal cryoglobulinemia). Finally, type III cryoglobulinemia involves only polyclonal immunoglobulins. Polyclonal IgM and IgG may form immune complexes (mixed polyclonal cryoglobulinemia) [5].

In this report, we describe the third case of MPGN type II with essential cryoglobulinemia without HCV infection which is usually defined in the literature as MPGN type II.
2. Case Presentation

A 61-year old woman was hospitalized at our department in November 2020, for reevaluation and second renal biopsy. She was previously diagnosed with MPGN in 2012 at another institution when clinical manifestation of disease included nephrotic proteinuria and hematuria without renal failure (proteinuria 5g/24h, urine: 15-20 red blood cells/high-power field). At that time, the patient was not examined in terms of cryoglobulinemia. Initially she was treated with pulses of methylprednisolone, then oral corticosteroids in a dose of 40mg until cessation when complete remission was achieved. In October 2017, immunosuppressive therapy (cyclophosphamide and prednisone) was reintroduced due to disease relapse (proteinuria 6g/24h, creatinine 162umol/L), until complete remission was achieved in October 2018. Thereafter, she continued with small doses of corticosteroids until September 2019, when she stopped therapy. She suffered from hypertension and hypothyroidism-both well regulated with medications.

In October 2020 she was evaluated for the first time at our institution due to reevaluation of the disease which was manifested by stable renal failure and sub-nephrotic proteinuria (2.37g/24h) when positive cryoglobulins were detected for the first time. At admission, her blood pressure was 140/80 mmHg, pulse rate 65/min, normal physical examination except for severe pretibial edema. No skin lesions were evident. Laboratory investigations indicated anemia with pseudothrombocytopenia (platelet counts in citrate-anticoagulated blood), azotemia with dyslipidemia and moderately elevated CRP (Table 1). Microscopic examination of the urine revealed 3-5 red and 3-5 white blood cells/high-power field (Table 1). Serological studies for anti-neutrophil cytoplasmic antibodies (ANCA) against myeloperoxidase and proteinase 3 and the anti-double stranded DNA antibodies were negative. Anti-hepatitis C antibodies were negative, as well as anti HIV antibodies and anti-hepatitis B surface antibodies. Serum immunoglobulin IgA were within normal limits as well as serum complement fractions. Serum and urine immunoelectrophoresis and immunofixation did not detect M protein or monoclonal IgM. Serum cryoglobulins were positive on two occasions but for technical reasons we were not able to define them more closely by electrophoresis.

| Variables            | Results  |
|----------------------|----------|
| Leukocytes, 10^9/L   | 7.2      |
| Erythrocytes, 10^12/L| 3.63     |
| Hemoglobin, g/dl     | 11.0     |
| Hematocrit, %        | 34.1     |
| Thrombocytes, 10^9/L | 102      |
| S-Creatinine, umol/L | 136      |
| S-Urea, mmol/L       | 10.9     |
| S-Cholesterol, mmol/L| 6.6      |
S-TRIGLYCERIDES, mmol/L          1.7
S-TOTAL PROTEINS, g/L            66
S-ALBUMINS, g/L                 38
CRP, mg/L                       24.3
IgA, g/L                        2.65
IgM, g/L                        0.89
IgG, g/L                        8.4
C3, g/L                         1.01
C4, g/L                         0.21

**Urine analysis**

| Result                      |
|-----------------------------|
| Color                       | Yellow                     |
| Specific gravity            | 1.015                      |
| pH                          | 5.0                        |
| Protein                     | 3+                         |
| Glucose                     | negative                   |
| Ketone                      | negative                   |
| Blood                       | +                          |
| Bilirubin                   | negative                   |
| Urobilinogen                | normal                     |
| Nitrite                     | negative                   |
| Leukocyte esterase          | negative                   |
| Urine sediment              | WBC 3-5, RBC 3-5           |
| 24h *urinary protein excretion* | 5.71; 2.46; 1.86; 1.88g/24h |

**Table 1:** Blood laboratory tests and urine analysis at admission.

Percutaneous renal biopsy was performed, and pathohistological analysis revealed: out of 6 glomeruli, one was completely sclerotic, but in others the lobulation was emphasized with a pronounced thickening of GBM which in some segments has a duplicated appearance. Mesangial segmental proliferation was present as well as rare mononuclear cells with altered surrounding interstitium. Groups of atrophic tubules with edematously altered interstitium and permeated mononuclear infiltrate in one part formed a larger aggregate. Blood vessels experienced wall thickening. Immunofluorescence microscopy: IgA-, IgG+, IgM-/-+, C1q+, C3+-C3++ staining in all specimens. The finding was compatible with the diagnosis of MPGN (see Figure 1).
Figure 1: Mesangial hypercellularity (which gives a lobulated appearance) and capillary wall thickening, diffuse duplication of the GBM in several segments of glomeruli (a, b - PAS stain, x 400). One glomerulus was globally sclerotic (c - PAS stain, x 200), interstitial fibrosis (best shown in Masson's trichrome stain (d)) and tubular atrophy and inflammation (c). (Thin dashed arrow-duplicated GBM, thick solid arrow-sclerotic glomerulus, thin solid arrow-lobular glomerulus, dashed arrow-mesangial modification).

Based on clinical, laboratory and histological evaluation, it was concluded that the patient had a MPGN with essential cryoglobulinemia. Since she had previously been treated with cyclophosphamide and prednisone, we commenced treatment with mycophenolate mofetil (2g/24h) divided into two doses. This therapy had a beneficial effect on the course of disease and the patient achieved partial remission and stable renal function for the last 3 months of follow-up.
3. Discussion

There are not many cases of essential mixed II cryoglobulinemia and MPGN described in the literature, especially in the absence of hepatitis C virus infection. Namely, in available literature we found only two cases: Taiwanese authors presented female patient of the same age and with very similar clinical presentation as our patient, but they confirmed cryoglobulinemia-monoclonal gammapathy afterward. Male patient presented by Indian authors was younger (34 years) and his laboratory findings have shown significantly higher levels of urea and creatinine, while urine analysis was very similar to that of our patient.

Initially, our patient was treated in another institution when she was diagnosed as MPGN but cryoglobulinemia was not considered at that time. Cryoglobulinemia was diagnosed after eight years, in October 2020, at our institution. In November 2020 the presence of cryoglobulins was confirmed for the second time and a re-biopsy was performed. Serum cryoglobulin testing involves a manual qualitative method. The test is based on the properties of cryoglobulins to group and precipitate in the cold, but dissolve at the high temperature. Negative results should be checked in 7 days. If cryoglobulins are present, additional testing is required that involves characterization and typing of the cryoglobulins. According to this, we repeated the test twice (both time positive), but more precise analysis of cryoglobulins was not available at that time. Still, considering the clinical presentation of disease, associated glomerulonephritis, typical histological finding, and absence any relevant ethiological factor linked to cryoglobulinaemia, we characterized her to have most likely essential cryoglobulinemia. In the further follow up of our patient, we should think about finding specific cause of cryoglobulinemia.

Apart from renal involvement, no other manifestation of EC was present. MPGN is the most frequent histologic finding in patients with essential cryoglobulinemia with subendothelial deposits. On immunofluorescence, deposits of immunoglobulin and complement are always present [8]. Immunofluorescence shows subendothelial and mesangial deposits of IgM, IgG, C3 and frequently C1q [8] like in our patient. Renal disease at presentation of cryoglobulinemia is apparent in less than 25% of patients, but develops in about 50% over time [8]. More than a half has proteinuria and/or hematuria. Nephrotic syndrome is diagnosed in 20% of patients and acute nephritic syndrome in 20% [7]. In our patient the disease was manifested by mild renal insufficiency with subnephrotic proteinuria. No standard treatment for essential cryoglobulinemia associated with MPGN treatment was suggested and decisions should be made purely on the basis of clinical experience. Acute nephritic and/or severe vasculitis flare-ups may be treated with high-dose of intravenous steroid pulses followed by a short-term course of oral prednisolone and cytotoxic drugs [8]. Patients who develop progressive renal disease are candidates for dialysis or transplantation. This patient had three partial remissions and last one was achieved by the protocol with mycophenolate mofetil. Still, we need longer follow-up period to establish the effect of such therapy and the course of disease. Since the therapy for MPGN with essential cryoglobulinemia is not standardized, further research in the field is needed.
References

1. Bassam Alchi and David Jayne. Membranoproliferative glomerulonephritis. Pediatr Nephrol 25 (2010): 1409-1418.
2. Naveed Masani, Kenar D Jhaveri, and Steven Fishbane. Update on Membranoproliferative GN. Clin J Am Soc Nephrol 9 (2014): 600-608.
3. Maurizio Salvadori and Giuseppina Rosso. Reclassification of membranoproliferative glomerulonephritis: Identification of a new GN: C3GN. World J Nephrol 5 (2016): 308-320.
4. Naveed Masani, Kenar DJhaveri, and Steven Fishbane. Update on Membranoproliferative GN. Clin J Am Soc Nephrol 9 (2014): 600-608.
5. Stéphanie Harel, Alexis Talbot. Cryoglobulinemia for use. Rev Prat 68 (2018): 1107-1112.
6. Anne Claire Desbois, Patrice Cacoub, David Saadoun. Cryoglobulinemia: An update in 2019. Revue du Rhumatisme 86 (2019): 241-248.
7. Hsu Jung-Hui, Fang Yu-Wei, Yang An-Hung, et al. Mixed cryoglobulinemic membranoproliferative glomerulonephritis due to monoclonal gammopathy of undetermined significance. Medicine 97 (2018): e12416.
8. Satish S, Rajesh R, George K, et al. Membranoproliferative glomerulonephritis with essential cryoglobulinemia. Indian J Nephrol 18 (2008): 80-82.

Citation: Dragana Marković, Petar Djurić, Aleksandar Janković, Ljiljana Bogdanović, Snežana Pešić, Nada Dimkovic, Radomir Naumović. Rare Glomerular Presentation of Essential Cryoglobulinemia without HCV Infection. Archives of Clinical and Medical Case Reports 5 (2021): 280-286.