

ANCA-negative pauci-immune rapidly progressive glomerulonephritis after COVID-19 – a case report

Nieme immunologicznie gwałtownie postępujące kłębuszkowe zapalenie nerek bez obecności przeciwciał ANCA po przebyciu COVID-19 – opis przypadku

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Abstract

Introduction: Rapidly progressive glomerulonephritis is a rare clinical condition characterised by rapid loss of renal function over a short period of time, nephritic syndrome, and crescents in renal biopsy. Pauci-immune rapidly progressive glomerulonephritis is usually associated with vasculitis, therefore skin, joints, lungs and nervous system may be involved. Numerous cases of pauci-immune rapidly progressive glomerulonephritis related with COVID-19 vaccines have been described in the literature, but there is little data on its occurrence after COVID-19 infection. **Case description:** We present a case of a 61-year-old female patient who was diagnosed with ANCA-negative pauci-immune rapidly progressive glomerulonephritis with nervous and respiratory system involvement within 5 months from COVID-19 infection. **Conclusions:** Pauci-immune rapidly progressive glomerulonephritis might be triggered by SARS-CoV-2 infection.

Keywords: SARS-CoV-2, rapidly progressive glomerulonephritis, pauci-immune, ANCA antibody-positive vasculitis (AAV)

Streszczenie

Wprowadzenie: Gwałtownie postępujące kłębuszkowe zapalenie nerek jest rzadkim zespołem klinicznym, objawiającym się szybką utratą czynności nerek w krótkim czasie, zespołem nefrytycznym i obecnością półksiężyców w biopsji nerki. Niememu immunologicznie (*pauci-immune*) gwałtownie postępującemu kłębuszkowemu zapaleniu nerek często towarzyszy zapalenie naczyń, a w przebiegu choroby może dochodzić do zajęcia skóry, stawów, płuc lub układu nerwowego. W literaturze opisano liczne przypadki niemego immunologicznie gwałtownie postępującego kłębuszkowego zapalenia nerek po szczepieniu przeciwko SARS-CoV-2, niewiele jest jednak danych odnośnie do występowania tej jednostki chorobowej po przebyciu infekcji COVID-19. **Opis przypadku:** Opisano przypadek 61-letniej pacjentki, u której w ciągu 5 miesięcy od przebycia COVID-19 rozpoznano nieme immunologicznie gwałtownie postępujące kłębuszkowe zapalenie nerek bez obecności przeciwciał ANCA z zajęciem układów nerwowego i oddechowego. **Wnioski:** Zakażenie SARS-CoV-2 może być czynnikiem spustowym dla rozwoju niemego immunologicznie gwałtownie postępującego kłębuszkowego zapalenia nerek.

Słowa kluczowe: SARS-CoV-2, gwałtownie postępujące kłębuszkowe zapalenie nerek, *pauci-immune*, zapalenie naczyń z obecnością przeciwciał ANCA

INTRODUCTION

Rapidly progressive glomerulonephritis (RPGN) is characterised by rapid (days or weeks) loss of renal function. Clinically, features of nephritic syndrome (haematuria with dysmorphic erythrocytes, subnephrotic proteinuria, hypertension, oedema) usually predominate. Destruction of the glomerular capillary wall and accumulation of epithelial cells in the Bowman's space, forming crescents, are the primary findings seen in renal histopathology⁽¹⁾. The pauci-immune RPGN (no deposits found in the kidney biopsy by immunofluorescence or electron microscopy) along with anti-GBM antibody-induced RPGN and RPGN associated with immune complexes are the most common types of RPGN⁽¹⁾.

The incidence of pauci-immune RPGN in the United States is estimated at 3.1/1,000,000, with significantly higher rates for individuals over 65 years⁽²⁾. Anti-neutrophil cytoplasmic antibodies (ANCA): antibodies against myeloperoxidase (MPO-ANCA/pANCA) associated with eosinophilic granulomatosis with vasculitis (formerly Churg–Strauss syndrome) and against proteinase 3 (PR3-ANCA/cANCA) associated with granulomatosis with polyangiitis (GPA, formerly known as Wegener's granulomatosis), constituting, together with microscopic vasculitis, the spectrum of ANCA-associated vasculitis (AAV), are found in the blood in 90% of patients with pauci-immune RPGN. Although 10% of patients with pauci-immune RPGN are ANCA negative, both cases are treated as one spectrum of disease and are subject to the

CASE REPORT

A 61-year-old woman with iatrogenic hypothyroidism, a history of thyroidectomy for multinodular goitre, treated with levothyroxine substitution, with a history of gout, otherwise untreated for chronic diseases, was admitted to the Department of Internal Medicine, Nephrology and Dialysis for acute kidney injury. Symptoms had occurred about two months earlier and included high blood pressure, headaches, sinus symptoms, as well as dark foamy urine. Five months prior to admission, the patient had a SARS-CoV-2 infection. On physical examination revealed peripheral oedema and elevated blood pressure. During subsequent admissions, the patient developed pain and oedema in both knee joints, as well as skin lesions on the face.

Initial laboratory workup indicated acute kidney injury without electrolyte disturbances, hypoalbuminaemia, hypoproteinaemia, normolipidaemia and normocytic anaemia; total urinalysis showed haematuria and proteinuria, with daily urinary protein excretion of 8.4 g (Tab. 1). Serology was run for systemic diseases and found no ANA, cANCA, pANCA, dsDNA, anti-GBM antibodies or decreased complement components (Tab. 2). Proteinogram showed no monoclonal protein (Tab. 3). HBV, HCV and HIV infections were excluded.

Renal ultrasound showed features of peripyramidal fibrosis and elevated resistance in segmental arterial flow. High-resolution computed tomography of the chest showed scar-like fibrotic areas, as well as reticular and band-like thickening in both lungs. The patient was consulted by an

Laboratory parameters	Month of hospital stay					
	I	II	IV	VI	VII	
Serum urea	73 H	102 H	61 H	52 H	32	mg/dL (15–43)
Serum creatinine	2.1 H	2.7 H	1.2 H	1.0 H	0.9	mg/dL (0.5–0.9)
Albumin – colorimetric method	3.2 L	3.0 L	3.7 L	4.2	3.5 L	g/dL (3.9–4.9)
Total protein	6.1 L	5.5 L	5.7 L	6.2 L	5.7 L	g/dL (6.4–8.3)
RBC	3.15 L	3.17 L	3.83	4.36	4.08	× 10 ¹² /L (3.5–5.5)
HGB	9.1 L	9.1 L	11.7	13.1	12.6	g/dL (11.0–18.0)
HCT	27 L	28 L	35	39	37	% (35–55)
Sodium	142	136	141	140	144	mmol/L (135–145)
Potassium	4.7	4.8	4.7	4.5	4.4	mmol/L (3.6–5.1)
24-hour urine protein test	4,049 H	8,487 H	1,166 H	1,757 H	–	mg/24 h (<150)

RBC – red blood cells; **HGB** – haemoglobin; **HCT** – haematocrit; **red colour, H** – result above the upper limit of normal; **blue colour, L** – result below the lower limit of normal; **grey colour** – reference values.

Tab. 1. Changes in laboratory parameters during hospital stay

same treatment regimens due to clinical and histopathologic similarities. In vasculitis, in addition to renal involvement, there may be also skin, joint, lung, peripheral nerve or skeletal muscle involvement⁽¹⁾.

Although many cases of ANCA-negative RPGN following the SARS-CoV-2 vaccine have been described in the literature, few reports have been published on its incidence after COVID-19^(3,4).

Complement components	Month of hospital stay			
	I	III	V	
C3	128	112	134	mg/dL (90–180)
C4	32	28	27	mg/dL (10–40)

Grey colour – reference values.

Tab. 2. Change in the levels of complement components during hospital stay

Total protein	6.1	g/dL (6.0–8.0)
Albumin (%)	44.9 L	% (52.0–65.1)
Alpha 1 (%)	3.8 H	% (1.0–3.0)
Alpha 2 (%)	17.4 H	% (9.5–14.4)
Beta 1 (%)	10.4 H	% (6.0–9.8)
Beta 2 (%)	10.2 H	% (2.6–5.8)
Gamma (%)	13.3	% (10.7–20.3)
Albumin	2.8 L	g/dL (3.1–5.2)
Alpha 1	0.2	g/dL (0.1–0.2)
Alpha 2	1.1	g/dL (0.6–1.2)
Beta 1	0.6	g/dL (0.4–0.8)
Beta 2	0.6 H	g/dL (0.2–0.5)
Gamma	0.8	g/dL (0.6–1.6)
A/G Ratio	0.8	
Red colour, H – result above the upper limit of normal; blue colour, L – result below the lower limit of normal; grey colour – reference values.		

Tab. 3. Proteinogram

ENT specialist, and no abnormalities were found; however, odontogenic foci of infection were detected in five teeth, which were extracted.

The patient was qualified for diagnostic renal biopsy, which described active pauci-immune-like glomerulonephritis with cellular crescents in 3/14 glomeruli (21.4%).

Further diagnostic workup also showed nervous system involvement. Magnetic resonance imaging (MRI) of the head showed multiple foci of increased signal in subcortical and periventricular white matter in both cerebral hemispheres and the midbrain, while electromyography showed axonal damage to the right sural nerve and possible damage to the motor fibres of both deep sagittal nerves at L4/S2.

Induction treatment with steroid therapy (methylprednisolone infusions with continued prednisone) and cyclophosphamide as per the CYCLOPS regimen, with a total of 5.1 g of cyclophosphamide administered, was implemented to induce remission. After six months of induction, maintenance treatment with mycophenolate mofetil was included, and prednisone was maintained. Although normalisation of renal function parameters, resolution of oedema and normalisation of blood pressure were achieved, other symptoms, such as arthralgia and dermatological problems, occurred. Repeated testing for cANCA and pANCA was negative. The patient started the vaccination cycle against SARS-CoV-2 (BioNTech Pfizer vaccine) already after developing symptoms (first vaccination dose 17 days after the kidney biopsy).

DISCUSSION

Typically, RPGN is clinically characterised by a nephritic syndrome. Although our patient presented with nephrotic proteinuria, the other symptoms (hypertension,

oedema, haematuria) were typical of nephritic syndrome. Histopathology is needed to confirm the diagnosis of RPGN. The patient's renal biopsy showed characteristic vascular changes and cellular crescents in >20% of the glomeruli. Less than 10% of crescents are not referred to as RPGN, as these cases have a different course and prognosis⁽⁵⁾. Some classifications limit the term RPGN, defining it as crescents in >50% of the glomeruli, while others also include cases with 10–50% glomerular involvement.

In addition to kidney problems, the patient also showed involvement of the lungs, nervous system, skin and joints, which is typical for vasculitis. The pulmonary lesions described in imaging and their symmetrical distribution in the peripheral parts are characteristic of pulmonary AAV⁽⁶⁾. The central nervous system lesions (foci of increased signal) were due to ischemic/haemorrhagic episodes as a result of damage to small vessels⁽⁷⁾. Peripheral neuropathy is also one of the classic features of vasculitis-related diseases, and it may be the only manifestation of the disorder in some patients⁽⁸⁾. Despite early immunosuppressive treatment, the disease progressed to involve other systems, giving rise to skin lesions and joint pain.

Repeated screening for ANCA was negative. Thus, the patient was among those 10% of patients with ANCA-negative pauci-immune RPGN.

The pathogenesis of ANCA-negative pauci-immune RPGN with systemic vasculitis is not clear. It has been suggested that it may be related to the presence of other types of ANCA that are not routinely screened (e.g., against cathepsin G, elastase, or other unidentified antigens), or disorders of the alternative complement pathway, such as decreased levels of C3 and C4 components, which were excluded in this case^(9,10).

Infectious agents, which dysregulate the immune system, may also play an important role in the pathogenesis of autoimmune diseases⁽¹¹⁾. Among these, odontogenic infections should be considered. Cases of vasculitis secondary to periodontitis or endodontic treatment have been reported in the literature⁽¹²⁾. In the described patient, five asymptomatic odontogenic foci of infection were removed during the course of treatment.

SARS-CoV-2 infection significantly affects the immune system, also by elevating the neutrophil-to-lymphocyte ratio (NLR), increasing the level of neutrophil extracellular traps (NETs), or by a cytokine storm⁽¹³⁾. Various types of autoantibodies have been detected in about 50% of patients after COVID-19 infection, compared to less than 26% of individuals in the control sample, with long virus persistence, epitope spread, and activation of the alternative complement pathway being factors predisposing to their production, which is particularly important in ANCA-negative pauci-immune RPGN with systemic vasculitis^(10,14). The literature also postulates that the mRNA vaccine against COVID-19 increases the risk of glomerulonephritis. Many cases of post-vaccine glomerulonephritis have been described on the basis of, for example, IgA nephropathy or AAV⁽¹⁵⁾.

However, Diebold et al. showed no association between the increased incidence of glomerulonephritis and the introduction of the mRNA vaccine against COVID-19⁽¹⁶⁾. The impact of vaccination can be excluded in the described patient, as she started the vaccination cycle already after the disease onset (17 days after kidney biopsy). Although many cases of GN without ANCA after SARS-CoV-2 vaccination have been described in the literature, little data is available on its occurrence after COVID-19⁽³⁾. It is possible that it was COVID-19 infection that triggered the patient's immune dysregulation and the onset of RPGN within 3 months.

CONCLUSIONS

ANCA-negative pauci-immune RPGN is a very rare disorder with an unclear pathogenetic background. Due to similar clinical course and renal histopathological picture to those seen in ANCA-positive vasculitis, these two conditions are often included in one spectrum and managed with the same treatment regimens. In the absence of ANCA in the pathogenesis, other factors should be considered, including infections that may cause immune dysregulation. The fact that our patient developed the disease within a few months after COVID-19 infection may indicate SARS-CoV-2 involvement as a trigger for pauci-immune RPGN, although the influence of other factors cannot be excluded. We suggest that a history of SARS-CoV-2 infection should be considered as a potential cause for the onset of RPGN.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

Author contribution

Writing of manuscript: NL, ZP, MR, SN. Critical review of manuscript: MR, SN. Final approval of manuscript: SN.

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