ŻEREK, Marta, SITAREK, Gracjan, PŁONKA, Wojciech, CHRUŚCICKI, Damian, BEDNARCZYK, Paulina, PELC, Marcin. Pulmonary-Renal Syndrome in the Elderly: Immunosuppressive Treatment – Case Report. Quality in Sport. 2024;24:54674. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.24.54674
https://apcz.umk.pl/QS/article/view/54674

The journal has had 20 points in Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 26.08.2024. Revised: 18.09.2024. Accepted: 07.10.2024. Published: 11.10.2024.

Pulmonary-Renal Syndrome in the Elderly: Immunosuppressive Treatment – Case Report

1. Marta Żerek [MŻ]

Uniwersytecki Szpital Kliniczny w Opolu, University of Opole, Poland

https://orcid.org/0009-0000-8505-1197

marta.zerek@gmail.com

2. Gracjan Sitarek [GS]

Uniwersytecki Szpital Kliniczny w Opolu, University of Opole, Poland

https://orcid.org/0009-0000-1856-4339

gracjans97@gmail.com

3. Wojciech Płonka [WP]

Independent Public Health Care Facility MSWiA in Opole, Poland

https://orcid.org/0009-0001-2519-1064

wojciech.plonka.72@gmail.com

4. Damian Chruścicki [DC]
Institute of Medical Sciences, University of Opole, Poland
dchru@protonmail.com
https://orcid.org/0009-0009-9887-4243

5. Paulina Bednarczyk [PB]
Szpital Uniwersytecki w Krakowie, Poland
https://orcid.org/0009-0009-3598-2490
bednarczyk.paulina@o2.pl

6. Marcin Pelc [MP]
Institute of Medical Sciences, University of Opole
https://orcid.org/0009-0006-3889-0223,
marcin.pelc@outlook.com

Abstract:
Pulmonary-renal syndrome is called alveolar hemorrhage accompanied by glomerulonephritis. The above condition can occur as a manifestation of ANCA-associated granulomatosis with vasculitis. The course of the disease varies from mild, limited inflammation to rapid progression with multi-organ changes that can be life-threatening. The mainstay of therapy is immunosuppression - both in the acute phase of the disease and after clinical improvement. Unfortunately, common causes of death in addition to complications of the disease include side effects of immunosuppressive treatment.

A 72-year-old man is transferred to the Nephrology Unit for acute kidney injury of unclear etiology. On the basis of clinical examination, laboratory and imaging studies, a diagnosis of systemic small vessel inflammation with c-ANCA occupying the kidneys, lungs and intestines was made. Due to acute respiratory failure, the patient was transferred to the ICU, where renal replacement therapy, plasmapheresis, steroid pulses and cyclophosphamide were administered. After clinical improvement, it was decided to continue cyclophosphamide therapy and monitor blood IgG levels. Unfortunately, 4 months later, the patient died of multiple organ failure caused by septic shock of bacterial etiology.

In the described case, age and comorbidities were the biggest risk factors for infectious complications of immunosuppression. The population is aging, so it is necessary to analyze the current standards of immunosuppressive treatment to improve the prognosis of the elderly.
Keywords: immunosuppression; pulmonary-renal syndrome; cyclophosphamide; elderly patients

Introduction:

Pulmonary-renal syndrome, characterized by alveolar hemorrhage along with inflammation of the kidney's glomeruli, can manifest as part of ANCA-associated granulomatosis with vasculitis. Granulomatosis with polyangiitis (GPA) progression ranges from mild, localized inflammation to swift advancement involving multiple organs, posing life-threatening risks. Immunosuppression stands as the primary approach in treatment. A common cause of death is not only complications of the disease, but also complications of immunosuppressive therapy.

With increasing life expectancy around the world and advances in the treatment of various immune-mediated diseases (IMDs), the number of elderly people with IMD will continue to rise. Treating elderly patients with chronic IMD can present some unique challenges. (Borren et al., 2019) As we age, the reactivity and efficiency of the immune system weakens. (Roży et al., 2016) Compared to younger populations, changes in drug pharmacokinetic properties, including absorption, distribution and excretion, may occur with age. (Borren et al., 2019) Older age is a risk factor for many comorbidities, such as cardiovascular disease, diabetes and cancer, which complicate the use of immunosuppressive therapy. (Borren et al., 2019)

Case report:

A man, aged 72, was admitted to the Nephrology Unit for acute kidney injury (AKI) of unclear etiology, unresponsive to previous treatment. On admission, the patient presented with dyspnea, rapidly increasing edema and signs of anemia. He had a history of multimorbidity, ischemic

heart disease, bronchial asthma, status post rectal tumor resection, and polypragmasia. Laboratory tests revealed anemia (Hb=7.9 g/dl), acute inflammation (CRP=150 mg/dl), AKI probably secondary to glomerulonephritis (creatinine=8.61 mg/dl; urea=173mg/dl; eGFR=6.52 ml/min/1.73m2). Additional examinations showed further abnormalities: USG - obliteration of renal corticospinal differentiation; Gastroscopy - erythematous gastropathy; Colonoscopy - gastrointestinal bleeding with indication for observation. It was decided to include renal replacement therapy and symptomatic treatment. During hospitalization, the patient's condition suddenly declined. It identified features of acute respiratory distress syndrome (ARDS). Imaging tests performed indicated alveolar hemorrhage. The patient required hospitalization in the ICU. Immunological tests were performed, which detected cANCA antibodies and antibodies against PR3. This allowed the diagnosis of pulmonary-renal syndrome secondary to systemic vasculitis with the presence of cANCA, also involving the intestinal mucosa. The patient was continued on renal replacement therapy and mechanical ventilation, plasmapheresis and immunosuppressive therapy were implemented. Pulses of methylprednisolone were administered and cyclophosphamide 0.6g was implemented. In addition, Immunoglobulin G monitoring was started as part of immunosuppression control. The patient showed good tolerance to cyclophosphamide. Stabilization of the patient's condition was achieved, renal function improved, renal replacement therapy was discontinued and disease remission occurred. Immunological tests were performed, which detected cANCA antibodies and antibodies against PR3. This allowed the diagnosis of pulmonary-renal syndrome secondary to systemic vasculitis with the presence of cANCA, also involving the intestinal mucosa. The patient was continued on renal replacement therapy and mechanical ventilation, plasmapheresis and immunosuppressive therapy were implemented. Pulses of methylprednisolone were administered and cyclophosphamide 0.6g was implemented. In addition, Immunoglobulin G monitoring was started as part of immunosuppression control. The patient showed good tolerance to cyclophosphamide. Stabilization of the patient's condition was achieved, renal function improved and renal replacement therapy was discontinued. Remission of the disease occurred. The decision was made to continue cyclophosphamide therapy and monitor the level of Immunoglobulin G in the blood. A renal biopsy indicated AKI probably secondary to Rapidly progressive glomerulonephritis (RPGN). Further treatment of the patient included consideration of discontinuing cyclophosphamide and starting mycophenolate mofetil therapy along with a reduction in steroid therapy. Unfortunately, the patient's condition became worse 4 months after starting treatment. The patient developed features of ARDS. The man was

diagnosed with bacterial etiology pneumonia. Increasing septic shock and multiple organ failure were observed. The patient developed sudden cardiac arrest that ended in death.

Discussion:

Older age is a risk factor for many comorbidities that complicate the use of immunosuppressive therapy. (Roży et al., 2016) In the case described here, the patient's age and comorbidities were the biggest risk factor for infectious complications of applied immunosuppression. The patient's death occurred as a result of acute respiratory failure due to bacterial pneumonia.

Early monitoring of immunoglobulin levels might help to identify the risk for developing infection. (Salminen et al., 2022) During the patient's immunosuppression, blood levels of Immunoglobulin G were monitored. IgG deficiency as a result of immunosuppression promotes the incidence of infections. Although the cutoff point for immunoglobulin levels that determines the occurrence of infectious complications has not been determined, a progressive decline in IgG levels is associated with an increased risk of infection. (Skórka et al., 2019) There is a need for more research in this area.

ANCA-positive small-vessel inflammation is characterized by necrotizing lesions of the vessel wall, which can be present in many organs and in the kidneys - glomerulonephritis with necrosis and thrombosis within them and with concomitant crescents. (Bułło et al., 2012) Patient mortality increases with age; the annual mortality rate in patients younger than 60 is 5%, and in those older than 60 it is 23%, and in patients older than 70 it is as high as 44%. (Bułło et al., 2012) Given the aging population, there is a need to analyze existing treatment standards in search of solutions that can improve prognosis among the elderly. In addition, the long-term course of the disease is fraught with chronic organ damage, the occurrence of relapses and side effects of therapy. Further research is needed to determine the most effective yet least toxic therapeutic options. (Bułło et al., 2012)

The treatment of choice for patients with rapidly progressive glomerulonephritis is the administration of immunosuppression, which means steroid pulses and cyclophosphamide combined with plasma exchange procedures. Only such treatment can eventually lead to improvement in renal function and cessation of renal replacement therapy. (Bułło et al., 2012)

Dosage of cyclophosphamide i.v. according to the patient's age and renal function (Szczeklik et al., 2021)		
Age (years)	Serum creatinine concentration	
	<300 umol/l	300-500 umol/l
<60	15 mg/kg	12,5 mg/kg
60-70	12,5 mg/kg	10 mg/kg
>70	10 mg/kg	7,5 mg/kg

Figure 1. Dosage of cyclophosphamide i.v. according to the patient's age and renal function.

The vasculitis associated with anti-neutrophil cytoplasmic antibodies (ANCA) can manifest as life-threatening pulmonary-renal syndrome. However, many prospective treatment studies have excluded patients with diffuse alveolar hemorrhage or severely impaired glomerular filtration rate. So optimal treatment in these cases is unclear. (Gulati et al., 2021) In the future, randomized trials of combination therapy with rituximab, cyclophosphamide and low-dose steroid therapy should also be conducted in patients with life-threatening symptoms. Cyclophosphamide remains the standard therapeutic option in generalized systemic disease. (Gulati et al., 2021) Biologic drugs represent the future of therapy, and are currently being used to treat the refractory form of the disease. (Comarmond et al., 2019) About 10% of patients show resistance to cyclophosphamide treatment. This particular group of patients requires intensive therapy with new-generation drugs, which include rituximab (Bułło et al., 2012). By binding selectively to the CD20 antigen, rituximab directly affects B lymphocytes, a key element for granulomatosis with vasculitis. (Sikorska et al., 2015) Data from the literature

provide evidence for the efficacy of rituximab in the treatment of granulomatosis with polyangiitis. (Alba et al., 2015), (Keogh et al., 2005)

In the elderly population, age-related physiological changes can result in clinically significant alterations in the pharmacokinetic parameters of immunosuppressants. (Jansen et al., 2012) Infections are an important cause of morbidity and mortality in elderly patients taking immunosuppressants. (Orlicka et al., 2013) More studies with older patients are required, as clinical trials have generally excluded the elderly. Close surveillance and collaboration is necessary by all practitioners involved in their care. (Ivulich et al., 2020), (Inoue et al., 2014), (Tesi et al., 1994) Aging aspects are in general not integrated into clinical immunosuppressive trials. Bacterial infections and malignancies are more frequent in the elderly. (Weinberger et al., 2012), (Lynch et al., 2009) Moreover, rates of diabetes mellitus are increasing with age. Of note, the use of immunosuppressive drugs has been shown to induce hyperglycemia and diabetes, both linked to inferior treatment outcomes, higher rates of remission rejections, and infections. Hence, older patients are more likely to suffer from adverse drug effects of their immunosuppression as reflected by higher rates of diabetes and de novo malignancies. Finally, older patients are dying more frequently due to bacterial infections compared to younger patients. (Krenzien et al., 2015)

Conclusions:

Pulmonary-renal syndrome is a life-threatening condition that can occur in the course of granulomatosis with polyangiitis. In addition to complications of the disease, complications of immunosuppressive treatment can be a reason for increased mortality. The elderly are particularly at risk of immunosuppression-related complications due to changes in the immune system and drug metabolism. In immune-mediated diseases, immunosuppression is often the only way to achieve disease remission, as in granulomatosis with polyangiitis. First-line treatment of this disease often involves cyclophosphamide, but new-generation drugs like rituximab are worth considering. Given the increasing number of elderly patients, research should be conducted on the safety of immunosuppressive therapy in this age group. Special attention should be paid to methods of individualizing drug dosage, monitoring the course and preventing complications of immunosuppressive therapy.

Author's contribution:

Conceptualization, Marta Żerek; methodology, Marta Żerek, Gracjan Sitarek; software, Marcin Pelc; check, Marta Żerek; formal analysis, Marta Żerek; investigation, Paulina Bednarczyk; resources, Gracjan Sitarek; data curation, Paulina Bednarczyk; writing - rough preparation, Damian Chruścicki; writing - review and editing, Wojciech Płonka; visualization, Damian Chruścicki; supervision, Wojciech Płonka; project administration, Marcin Pelc;

All authors have read and agreed with the published version of the manuscript.

Conflict of interest: The author declare no conflict of interest.

Funding statement: No external funding was received to perform this review

Statement of institutional review committee: not applicable

Statement of informed consent: not applicable

Statement of data availability: not applicable

References

Alba, M. A., & Flores-Suarez, L. F. (2015). Rituximab as maintenance therapy for ANCA associated vasculitis: How, when and why? *Reumatologia Clinica*. https://doi.org/10.1016/j.reuma.2015.06.002

Borren, N. Z., & Ananthakrishnan, A. N. (2019). Safety of biologic therapy in older patients with immune-mediated diseases: A systematic review and meta-analysis. *Clinical Gastroenterology and Hepatology*, 17(9), 1736-1743.e4. https://doi.org/10.1016/j.cgh.2018.12.032

Bułło, B., & Rutkowski, B. (2012). ANCA-dodatnie zapalenia małych naczyń—współczesne aspekty terapeutyczne. *Renal Disease and Transplantation Forum*, 5(1).

Comarmond, C., & Cacoub, P. (2014). Granulomatosis with polyangiitis (Wegener): Clinical aspects and treatment. *Autoimmunity Reviews*, 13(11), 1121–1125. https://doi.org/10.1016/j.autrev.2014.08.017

Gulati, K., Edwards, H., Prendecki, M. T., Cairns, T. D., Condon, J., Galliford, J., et al. (2021). Combination treatment with rituximab, low-dose cyclophosphamide, and plasma exchange for severe antineutrophil cytoplasmic antibody-associated vasculitis. *Kidney International*, 100(6), 1316-1324. https://doi.org/10.1016/j.kint.2021.07.026

Inoue, S., Suzuki, K., Komori, Y., Morishita, Y., Suzuki-Utsunomiya, K., Hozumi, K., ... & Sato, T. (2014). Persistent inflammation and T cell exhaustion in severe sepsis in the elderly. *Critical Care*, 18, 1-13.

Ivulich, S., & Snell, G. (2020). Long-term management of elderly patients taking immunosuppressive medications. *Australian Journal of General Practice*, 49(3), 100–106. https://doi.org/10.31128/ajgp-10-19-5137

Jansen, P. A., & Brouwers, J. R. (2012). Clinical pharmacology in old persons. *Scientifica (Cairo)*, 2012, 723678. https://doi.org/10.6064/2012/723678

Keogh, K. A., Wylam, M. E., Stone, J. H., & Specks, U. (2005). Induction of remission by B lymphocyte depletion in eleven patients with refractory antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis and Rheumatism*, 52(1), 262–268. https://doi.org/10.1002/art.20718

Krenzien, F., ElKhal, A., Quante, M., Rodriguez Cetina Biefer, H., Uehara, H., Gabardi, S., & Tullius, S. G. (2015). A rationale for age-adapted immunosuppression in organ transplantation. *Transplantation*, 99(11), 2258-2268. https://doi.org/10.1097/TP.0000000000000842

Lynch, H. E., Goldberg, G. L., Chidgey, A., Van den Brink, M. R. M., Boyd, R., & Sempowski, G. D. (2009). Thymic involution and immune reconstitution. *Trends in Immunology*, 30, 366–373.

Orlicka, K., Barnes, E., & Culver, E. L. (2013). Prevention of infection caused by immunosuppressive drugs in gastroenterology. *Therapeutic Advances in Chronic Disease*, 4(4), 167–185. https://doi.org/10.1177/2040622313485275

Roży, A., & Chorostowska-Wynimko, J. (2016). Układ immunologiczny osób starszych. *Alergia*, 1, 29-33.

Salminen, A. (2022). Clinical perspectives on the age-related increase of immunosuppressive activity. *Journal of Molecular Medicine (Berl)*, 100(5), 697-712. https://doi.org/10.1007/s00109-022-02193-4

Sikorska, D., Wytyk-Nowak, A., Mojs, E., Szynka, A., & Samborski, W. (2015). Ziarniniakowatość z zapaleniem naczyń, z zajęciem ośrodkowego układu nerwowego i serca skutecznie leczona rytuksymabem. *Forum Rheumatology*, 1(1), 43–46. https://journals.viamedica.pl/rheumatology_forum/article/view/43336/34985

Skórka, K., et al. (2019). Zaburzenia układu immunologicznego u chorych na przewlekłą białaczkę limfocytową. *Advances in Hygiene & Experimental Medicine / Postępy Higieny i Medycyny Doświadczalnej*, 73, 117–132. https://doi.org/10.5604/01.3001.0013.0876

Szczeklik, A., Gajewski, P., et al. (2021). *Interna Szczeklika* (12th ed.). Kraków: Wydawnictwo Medycyna Praktyczna.

Tesi, R. J., Elkhammas, E. A., Davies, E. A., Henry, M. L., & Ferguson, R. M. (1994). Renal transplantation in older people. *The Lancet*, 343(8895), 461-464.

Weinberger, B., & Grubeck-Loebenstein, B. (2012). Vaccines for the elderly. *Clinical Microbiology and Infection*, 18(Suppl 5), 100–108.