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Did COVID-19 benefit a patient with microscopic polyangiitis?

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Abstract

Microscopic polyangiitis (MPA) is a necrotizing inflammation that affects almost exclusively small vessels, i.e. capillaries, arterioles and venules. It manifests most often in individuals aged 50–60. It is a systemic disease that most commonly involves the kidneys and lungs. Rapidly progressive glomerulonephritis is the most important clinical presentation of the disease. It affects 80–100% of patients and most often leads to renal failure. The diagnosis of MPA is based on the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2022 classification criteria.

Nasal involvement in the form of bloody nasal discharge, nasal crusting or sino-nasal congestion, blockage, damage or perforation of the nasal septum are clinical criteria and refute the diagnosis of MPA (–3).

Laboratory criteria are the perinuclear antineutrophil cytoplasmic antibody (pANCA) or anti–myeloperoxidase-ANCA (MPO-ANCA) positivity (6), cytoplasmic ANCA (cANCA) or anti–proteinase 3 ANCA (PR3-ANCA) positivity (–1), eosinophil count ≥ 1000/μL (–4); imaging criteria are lung fibrosis or interstitial lung disease (3), and pauci-immune glomerulonephritis represents histological criteria (3).

A score ≥ 5 in six categories is required to meet the classification criteria [1].

Key words: microscopic polyangiitis; tocilizumab; COVID-19

Case report

We report a case of microscopic polyangiitis complicated by acute kidney injury, which was diagnosed and treated in 2020, i.e. during the onset of the COVID-19 pandemic in Poland. A 46-year-old female patient reported to the Hospital Emergency Department in June 2020 with complaints of stabbing chest pain, breathlessness, nausea and vomiting. She has been on L-thyroxine due to hypothyroidism and otherwise had no chronic illnesses and taken no other medication. Physical examination revealed a subfebrile state and signs of pharyngitis; otherwise, no other irregularities. Laboratory results were normal, and the electrocardiogram (ECG) was also within the normal range. An upper respiratory tract infection was diagnosed, and antibiotic therapy and analgesic treatment were recommended. Symptoms recurred after approximately two weeks, and the patient was re-admitted to the hospital for persistent pain in the sternal region, exacerbated by physical activity and breathing, accompanied by breathlessness and dizziness. No abnormalities were found during the physical examination and additional examinations. Another analgesic treatment was started, and ad hoc hydroxyzine was administered, yielding improvement. After another three weeks, in July 2020, the patient was referred by her GP to the internal medicine department for diagnosis of a subfebrile state, epigastric pain and loss of appetite. The patient also continued to complain of recurrent breathlessness and a paroxysmal cough. Laboratory investigations revealed microcytic anaemia [lowest haemoglobin (Hb) — 8.1 g/dL], thrombocytosis (up to 646,000/μL), elevated inflammatory markers [C-reactive protein (CRP) — up to 87 mg/L], D-dimers — 2,529 ng/mL, rheumatoid factor above the upper limit (29.3 IU/mL). A computed tomography (CT) scan of the chest with contrast on 16 July 2020 revealed fluid in both pleural cavities and atelectasis within segment 9 of the left lung. Echocardiography (ECHO) showed pericardial fluid and mild mitral valve insufficiency without segmental myocardial contractility abnormalities. Abdominal ultrasound (USG) revealed hepatosplenomegaly, and gastroscopy revealed a sliding hiatal hernia. Antibiotic therapy, corticosteroid therapy and iron supplementation were initiated. The applied treatment resulted in clinical improvement, and the patient was discharged home in overall good condition. Scheduled follow-up laboratory tests (after three weeks) showed persistent microcytic anaemia [Hb — 10.4 g/dL with mean corpuscular volume (MCV) — 73.1 fL] and features of active urine sediment. A contrast-enhanced chest CT on 13 August 2020 indicated complete regression of the pericardial and pleural effusions. After another three months, in November 2020, the patient was re-admitted

to the internal medicine ward due to increasing exertional dyspnoea, subfebrile states and an intermittent chest skin rash accompanied by joint pain and a stabbing sensation in the chest. Physical examination revealed bilaterally muffled vesicular murmur; laboratory tests revealed severe anaemia (Hb — 6.6 g/dL with MCV of 75.4 fL), elevated inflammatory markers (CRP — 34.46 mg/L, procalcitonin (PCT) – 0.19 ng/mL, erythrocyte sedimentation rate (ESR) — 62 mm/h), haematuria, abnormal proteinogram profile (increased alpha-1 globulin, beta-2 globulin). A contrast-enhanced CT scan of the chest performed at that time (November 2020) revealed ground-glass opacity of both lung fields, a small amount of fluid in the pleural cavities, and enlarged hilar and mediastinal lymph nodes. Abdominal ultrasound showed persistent splenomegaly and increased renal echogenicity. After the patient was transfused with 3 units of packed red blood cells, a suspicion of systemic lupus erythematosus was raised, and she was referred to the Department of Rheumatology and Systemic Connective Tissue Diseases at the University Hospital No. 2 in Bydgoszcz for further diagnosis and treatment.

During the hospital stay, in addition to the aforementioned symptoms, the patient reported several instances of expectoration with a small amount of blood. Due to the COVID-19 pandemic in Poland, the patient was tested twice by polymerase chain reaction (PCR) in the first days of hospitalization for SARS-CoV-2 infection, and the results were negative. Laboratory tests showed hypoalbuminaemia and impaired renal function (creatinine — 1.47 mg/dL). Urinalysis indicated proteinuria and numerous fresh and dysmorphic erythrocytes; immunofixation revealed IgG kappa protein, elevated markers of human epididymis protein 4 (HE4), and cancer antigen 125 (CA125). Immunological tests determined the presence of antinuclear antibodies (ANA), ANA3, including anti-double stranded DNA (dsDNA) antibodies, anti-native DNA (nDNA) antibodies, antineutrophil cytoplasmic antibodies (ANCA): perinuclear ANCA (pANCA) and cytoplasmic ANCA (cANCA), anticardiolipin antibodies, anti-B2-glycoprotein antibodies, anti-SARS-CoV-2-IgG antibodies. The presence of pANCA was confirmed, and the others were absent. Abdominal ultrasound revealed a hyperechogenic renal cortex and splenomegaly, pleural ultrasound revealed fluid in both pleural cavities, and ECHO showed no pericardial fluid. The patient had a haematological consultation, finding no haematological disease, and a gynaecological consultation [after ultrasound and pelvic magnetic resonance imaging (MRI) without contrast, the patient was qualified for further follow-up in the gynaecological oncology clinic].

Considering the complex clinical picture, the patient met the classification criteria for microscopic polyangiitis (MPA) according to the 2022 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR): p-ANCA or anti-MPO-ANCA — 6 points, lung fibrosis or interstitial lung disease — 3 points.

A sudden deterioration of renal function [an increase in creatinine to 2.37 mg/dL (glomerular filtration rate (GFR) – 24 mL/min) and a decrease in haemoglobin to 6.4 g/dL] was noted on day 3. The patient was given pulses of methylprednisolone (Solu-Medrol) at 1 g each for three days and transfused with 4 units of irradiated leukocyte-depleted RBCs with no complications. Intravenous hydration was carried out under daily fluid balance control. It should be noted that one of the reasons for the sudden deterioration of renal function may have been the administration of contrast three times during chest CT examinations over four months (contrast-induced nephropathy). Due to the continuous decrease in Hb concentration, the patient was periodically transfused with irradiated leukocyte-depleted RBCs (11 units of irradiated leukocyte-depleted RBCs during the entire hospital stay). On day 14 of hospitalization, the patient developed a fever of up to 38.5ºC. Blood cultures, urine cultures and a swab for SARS-CoV-2 infection were all negative. Due to deteriorating renal parameters and an increase in daily protein excretion (from 0.82 g/24 h to 1.66 g/24 h), it was decided to include further pulses of methylprednisolone at 500 mg each, a total of 3 (1,500 mg total) followed by prednisone at a dose of 40 mg a day. The patient was then qualified for therapeutic plasmapheresis. Due to increased inflammatory parameters [CRP, interleukin 6 (IL-6), PCT], broad-spectrum antibiotic therapy was included. A positive result for SARS-Cov-2 was obtained on the following day, i.e. 16 December 2020. The patient's condition was deteriorating. Her saturation decreased to about 88%, with a value of about 95% achieved after oxygen therapy at a flow rate of 2 L/min was initiated. Given the patient's worsening clinical condition, high-resolution computed tomography (HRCT*)* images (bilateral diffuse ground-glass opacity areas in most lungs, parenchymal consolidation in the right middle lobe and right lower lobe, significant and most intense in segments 6, 9, 10 and segment 6 of the left lung) showed progression of lesions in the right lung and regression of lesions in the left lung compared with the previous month's examination. It was difficult to conclusively determine whether the progression of pulmonary lesions was a result of SARS-CoV 2 infection or increased MPA activity with significantly elevated inflammatory parameters and a high increase in IL-6 levels (from 11.7 pg/mL to > 284 pg/mL). Following an application by the Head of the Department of Rheumatology and urgent approval from the bioethics committee for treatment with tocilizumab, despite the lack of drug registration for MPA, the

first dose of 400 mg of intravenous tocilizumab was administered. On the following day, due to lack of improvement and persistent respiratory failure, another dose of tocilizumab (400 mg) was administered, followed by plasma from a recovered patient and intravenous immunoglobulins (30 g each for three days). In the following days of the hospital stay, significant improvement in the clinical condition and stabilization of inflammatory parameters, as well as improvement in renal parameters, were observed. The patient was again admitted to the hospital a month later (January 2021) — laboratory tests indicated stable anaemia (Hb — 9.0 g/dL), thrombocytopenia [platelets (PLT) — 103 G/L], improving renal function (creatinine 1.55 mg/dL with GFR 41 mL/min and features of active urine sediment). The proteinogram was normal, and immunofixation revealed no monoclonal protein. The patient had another haematological consultation, and there were no indications for an extended diagnosis, including a punch biopsy. The patient was hospitalized several times to continue intravenous methylprednisolone pulse therapy; the oral dose of prednisone was gradually reduced, and the dose of mycophenolate mofetil (MMF) was maintained (2 g/day). Subsequent hospitalizations brought further improvement in well-being, resolution of reported complaints, gradual increase in haemoglobin levels (Hb — 11.4 g/dL -> 12 g/dL -> 12.5 g/dL) -> 12.2 g/dL), improvement in renal function (1.18 mg/dL with eGFR 57 mL/min/1.73 m^2 -> 1.0 mg/dL with eGFR 69 mL/min/1.73 m^2 -> 0.95 with eGFR 73 mL/min/1.73 m^2) and decreasing proteinuria [daily urine protein] – 0.68 g/24 h -> 0.58 g/24 h -> 1.36 g/24 h (MMF dose increased) -> 0.92 g/24 h -> 0.7 g/24 h -> 0.37 g/24 h -> 0.24 g/24 h -> 0.13 g/24 h). A follow-up HRCT of the lungs (June 2021) showed significant resolution of the lesions (Fig. 1) — single adhesions at the base of the right lung; otherwise, lungs without increased parenchymal density or interstitial lesions. It was decided to discontinue methylprednisolone pulse therapy, and the oral doses of prednisone and MMF were gradually reduced until they were discontinued entirely.

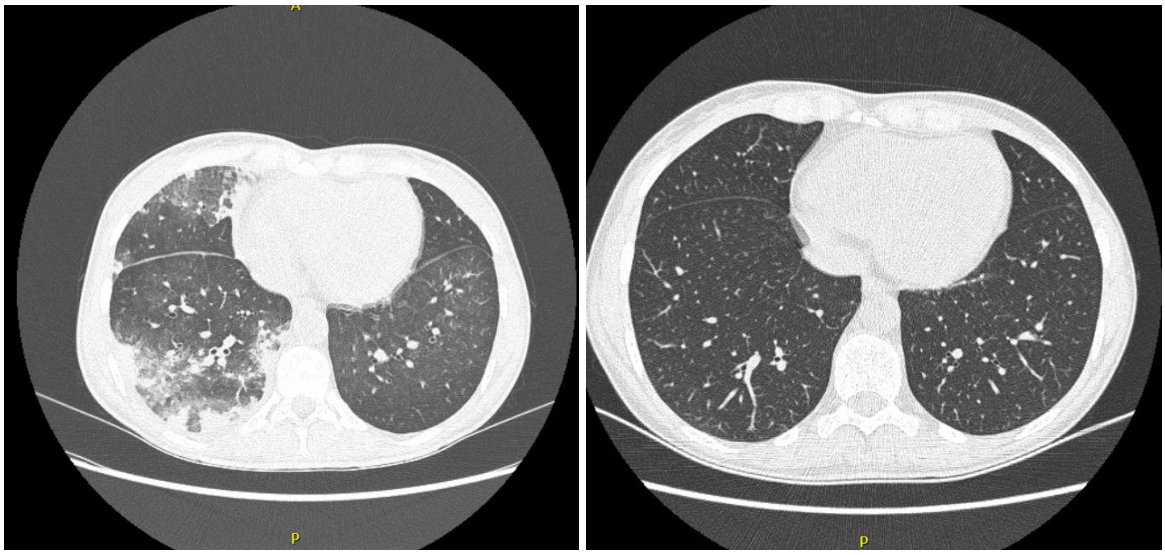

Figure 1. High-resolution computed tomography (HRCT) of the lungs of July 2020 (left) and January 2021 (right)

Discussion

MPA is a necrotizing vasculitis involving mainly small vessels (i.e. capillaries, venules or arterioles). Small and medium-sized arteries may also be affected by the inflammatory process in some patients. The disease primarily affects the kidneys (necrotizing glomerulonephritis) and the lungs (pulmonary capillaritis). Renal involvement, which may be the only symptom, is clinically apparent as rapidly progressive glomerulonephritis [2].

The cause of the disease is unknown. ANCAs are thought to be involved in the pathogenesis of the disease. The coexistence of other genetic or infectious factors appears to contribute to the onset of the disease [3].

MPA manifests slightly more frequently in men than in women (male-to-female ratio is 1.8:1), and the average age at onset is 50–60.

More than 70% of patients present with systemic symptoms such as fever or weight loss at diagnosis. Symptoms may be non-specific and present many months before the diagnosis is made (e.g. flu-like symptoms or joint pain). Renal involvement, marked by rapidly progressive glomerulonephritis (RPGN), is the main clinical feature of MPA. Previous studies have shown that 80–100% of patients with MPA develop renal symptoms ranging in severity from asymptomatic active urine sediment to end-stage renal failure requiring dialysis. The most common clinical signs of renal involvement are proteinuria (in the nephrotic range affecting up to 50% of patients) and haematuria. Renal sections show focal segmental necrotizing glomerulonephritis (up to 100% of patients) with crescents present (in about 90%

of patients). Immunofluorescence revealed minimal immunoglobulin or complement deposition in the glomeruli and renal vessels. The changes observed in the renal biopsy are similar in the three types of ANCA-associated vasculitis (MPA, WG and CSS) and therefore cannot be used to differentiate between these conditions.

Pulmonary involvement affects approximately 25–55% of patients and may manifest as haemoptysis or haemorrhage into the alveolar lumen, pleural effusion, pulmonary oedema, pleuritis or interstitial fibrosis. The classic pulmonary manifestation of MPA is diffuse alveolar haemorrhage due to pulmonary capillaritis (12–55% of patients), and common symptoms are dyspnoea, cough, haemoptysis and pleuritic chest pain. In patients with alveolar haemorrhage, chest imaging studies show patchy bilateral airspace opacification, usually involving both the upper and lower lung fields. The most common finding on lung HRCT is a ground-glass image found in more than 90 % of patients, which is consistent with alveolar haemorrhage and capillaritis. Skin lesions present in 30–60% of patients, most commonly in the form of palpable purpura, which affects 30–40% of patients.

Other symptoms may include livedo reticularis, nodules, urticaria and skin ulceration with necrosis. Skin specimens show features of leukocytoclastic vasculitis.

The most common gastrointestinal symptom is abdominal pain, which occurs in 30–58% of patients, while gastrointestinal bleeding affects up to 21–29% of patients.

Nervous system involvement affects 37–72% of patients and most commonly manifests as peripheral neuropathy with polyneuritis and distal symmetric polyneuropathy. Central nervous system symptoms account for 17–30% of the nervous system involvement observed in MPA and may present as haemorrhagic stroke, ischaemic stroke and meningitis.

The diagnosis of MPA is based on a cumulative analysis of symptoms, as no classification criteria for the disease have yet been developed.

There is also currently no laboratory test that has diagnostic specificity for MPA. As ANCAs are only detected in 50–75% of patients with this disease, their absence does not exclude this diagnosis. ANCAs associated with MPA generally have a perinuclear staining pattern (pANCA) caused by myeloperoxidase antibodies (MPO-ANCA), which can be detected by enzyme-linked immunosorbent assay (ELISA). Immunofluorescence has a higher sensitivity, but ELISA has a higher specificity for diagnosing MPA. Unfortunately, none of the tests are specific for MPA, as these antibodies are found in patients with other ANCA-associated vasculitis. Laboratory tests usually reveal elevated inflammatory markers (ESR, CRP), normochromic and normocytic anaemia, leukocytosis, and thrombocytosis [4].

Based on the 2022 EULAR recommendations for the management of ANCA-associated vasculitis, a combination of corticosteroid therapy and rituximab (RTX) or cyclophosphamide (CYC) is indicated to induce remission in patients with newly diagnosed or recurrent MPA [or granulomatosis with polyangiitis (GPA)] with organ- or life-threatening disease. RTX is preferred for relapses. In order to induce remission of non-organ or life-threatening MPA, a therapy combining corticosteroids and RTX is recommended. Methotrexate (MTX) or MMF may be considered as an alternative to RTX. As part of remission induction regimens in MPA (and GPA), treatment with oral corticosteroids at an initial dose of 50–75 mg prednisolone equivalent/day is recommended, depending on body weight, with gradual dose reduction until a dose equivalent to 5 mg prednisolone per day is reached for four to five months.

Plasmapheresis may be considered as part of therapy to induce remission in patients with serum creatinine levels > 300 μmol/L due to active glomerulonephritis. It is not recommended to routinely use plasmapheresis to treat alveolar haemorrhage.

RTX therapy is indicated to maintain MPA (and GPA) remission after remission induction with RTX or CYC; alternatively, azathioprine (AZA) or MTX may be considered, with a recommendation to continue treatment for 24–48 months after remission induction. In patients with relapsed disease or at increased risk of relapse, longer treatment duration should be considered, but patient preference and the risk of further immunosuppression should be taken into account [5].

Advances in clinical research have enabled the identification of new potential targeting molecules, including B-cell activating factor (BAF), C5a receptor and IL-6 receptor.

IL-6 is an inflammatory cytokine that is also involved in the pathogenesis of ANCA-associated vasculitis (AAV). Results to date suggest that IL-6 blockade is therapeutically effective in patients with AAV. Although results of ongoing or planned clinical trials are unavailable, the clinical development of targeted molecular therapy for MPA is promising and expected to rapidly change existing treatment strategies. Reducing or eliminating the use of corticosteroids would reduce many distant side effects and improve long-term outcomes [6].

The presented case of a patient in the era of the COVID-19 pandemic posed both diagnostic and therapeutic difficulties. It was difficult to conclusively determine whether the deterioration of the patient's condition, the increasing inflammatory parameters and the progression of lung lesions with a concomitant positive test for SARS-CoV-2 infection were the result of a coexisting infection or increased MPA activity. This, in turn, hindered the decision to implement tocilizumab therapy. The improvement in well-being, stabilization of inflammatory markers and complete regression of interstitial lung lesions, in addition to the

persistent long-term remission of the disease despite completion of corticosteroid and MMF therapy, may indicate that tocilizumab was effective in treating both COVID-19 and MPA.

Ethics statement

Not needed.

Author contributions

Conceptualization: K.G.S., D.J., review: K.G.S., D.J., A.G.P., T.B.; formal analysis: K.G.S., D.J., A.G.P., T.B.; resources: K.G.S.; writing — original draft: K.G.S.; writing — review and editing: K.G.S., D.J., A.G.P., T.B.; visualization: K.G.S.; supervision: K.G.S., D.J., A.G.P., T.B. All authors have read and agreed to the published version of the manuscript.

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Not needed.

Conflict of interest

The authors declare no conflict of interest.

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