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Case Report

A case of microscopic polyangiitis with interstitial pneumonia after coronavirus disease-2019 infection, evidenced by positivity for multiple autoantibodies

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ABSTRACT

Anti-neutrophil cytoplasmic antibody-associated vasculitis is triggered by infection, dust exposure, and drugs. A 73-year-old male presented with dyspnea. Severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infection was confirmed upon admission. Exacerbation of interstitial pneumonia and renal dysfunction were observed. Analysis revealed positivity for myeloperoxidase-anti-neutrophil cytoplasmic antibody, other anti-aminoacyl transfer RNA synthetase antibodies, and anti-melanoma differentiation-associated gene 5. Renal biopsy confirmed crescentic glomerulonephritis, leading to the diagnosis of microscopic polyangiitis. Combination therapy with prednisolone and cyclophosphamide was initiated, resulting in improved respiratory and renal failure. There is a potential association between SARS-CoV-2 infection and the onset of autoimmune diseases.

1. Introduction

Antineutrophil cytoplasmic antibody-associated (ANCA-associated) vasculitis is a group of diseases characterized by necrotizing vasculitis without immune complex deposition in small vessels. It includes three diseases, namely microscopic polyangiitis (MPA), granulomatosis polyangiitis, and eosinophilic polyangiitis granulomatosis with polyangiitis. In MPA, analysis for myeloperoxidase-ANCA (MPO-ANCA) often yields positive results, and the lungs and kidneys are the most commonly affected organs.

Alveolar hemorrhage and interstitial pneumonia are critical conditions. In this report, we describe a case of a patient with MPA who tested positive for anti-melanoma differentiation-associated gene 5 (anti-MDA-5) and anti-aminoacyl-transfer RNA synthetase (anti-ARS) antibodies. This case may have manifested following severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infection.

2. Case presentation

A previously healthy 73-year-old male visited a local hospital with dyspnea. Chest computed tomography performed 3 months earlier revealed the presence of interstitial shadows in the lung. Laboratory tests were positive for MPO-ANCA (5.4 U/mL, normal value < 3.5 U/mL) and anti-ARS antibodies (169 index level, normal value < 25 index level), while serum creatinine level (0.86 mg/dL, normal value 0.65–1.07 mg/dL) was normal. He did not attend the hospital afterward, but he visited our hospital due to worsening

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dyspnea. He had a 52 pack-year smoking history and no history of alcohol consumption, allergies, autoimmune diseases, respiratory diseases, or kidney diseases.

On physical examination, fine crackles were heard in bilateral lower lung fields on auscultation. There was no findings of clubbed fingers, mechanic's hands, Gottron's sign, erythema, or induration of the lower legs. Chest X-ray examination showed diffuse ground-glass shadows in bilateral lower lung fields. Chest computed tomography revealed the presence of ground-glass opacities with a reticular shadow and left pleural effusion in bilateral lung bases (Fig. 1A).

On admission, the patient tested positive for SARS-CoV-2 using polymerase chain reaction. He required isolation in a private room for 8 days, and treated with ceftriaxone due to the possibility of bacterial pneumonia. Laboratory tests on admission showed elevated levels of MPO-ANCA (163 U/mL), anti-ARS antibody (174 index level), anti-MDA-5 antibody (73 index level, normal value < 32 index level), and serum creatinine (1.37 mg/dL).

We considered ANCA-associated vasculitis, anti-MDA-5 antibody-positive interstitial pneumonia, and anti-ARS antibody syndrome in the differential diagnosis. Among ANCA-associated vasculitis, we suspected MPA over GPA or EGPA due to the higher prevalence of PR3-ANCA positivity in Japanese patients the absence of nasal lesions, the lack of nodules or cavitary lesions on chest CT in GPA, the absence of preceding asthma symptoms seen and the lack of eosinophilia in blood tests in EGPA. Anti-MDA-5 antibody-positive interstitial pneumonia was deemed less likely due to the low titer of anti-MDA-5 antibodies and the slow, atypical progression of interstitial shadows. Anti-ARS antibody syndrome was also considered atypical due to the presence of hematuria and renal dysfunction.

A renal biopsy revealed crescent formation in some glomeruli and a pauci-immune type without immune complexes or complement deposition. His renal lesions were diagnosed as crescent-forming glomerulonephritis (Fig. 2).

Applying diagnostic criteria for MPA in Japan [1], definite MPA diagnosis was made based on fulfilled the following four criteria: rapidly progressive glomerulonephritis, interstitial pneumonia, major histological findings, and laboratory findings of MPO-ANCA and elevated C-reactive protein.

Thus, treatment with prednisolone (50 mg/day) was started on day 12 of admission, followed by intravenous administration of cyclophosphamide (700 mg) on day 17.

Following the initiation of treatment with prednisolone, and cyclophosphamide, the levels of C-reactive protein, creatinine, and MPO-ANCA decreased, and ground-glass opacities of lung improved (Fig. 1B, Table 1).

At 10 months after hospitalization, the MPO-ANCA titer has improved to within the normal range, serum creatinine is within the normal range, and there has been no worsening of interstitial shadows.

3. Discussion

In the present case, MPO-ANCA levels increased due to SARS-CoV-2 infection, leading to the onset of MPA. Since June 2022, nine cases of ANCA-associated vasculitis post SARS-CoV-2 infection have been reported (Table 2) [2–10]. The male-to-female ratio was 7:2 (mean age: 46.2 years): seven and two cases were positive for proteinase 3-ANCA and MPO-ANCA respectively. Onset from COVID-19 infection ranged from simultaneous to 3 months. Prednisolone was administered in all cases, with or without a combination of cyclophosphamide and rituximab.

In recent years, it has been reported that neutrophil extracellular traps (NETs) induced by SARS-CoV-2 infection can trigger ANCA-associated vasculitis. The production of ANCA involves several stages. Generally, it can be divided into the following steps: initial stimulation and antigen presentation, priming of neutrophils, formation and sustenance of NETs, antigen presentation to NETs by dendritic cells, and ANCA production by B cells. Additionally, excessive NETs can lead to self-tolerance to MPO and PR3[11].

Infection with SARS-CoV-2 leads to a cytokine storm [12], causing overactivation of neutrophils and excessive production of ANCA along with the formation of NETs. This process contributes to the formation of MPO-ANCA and PR3-ANCA. Consequently, vascular

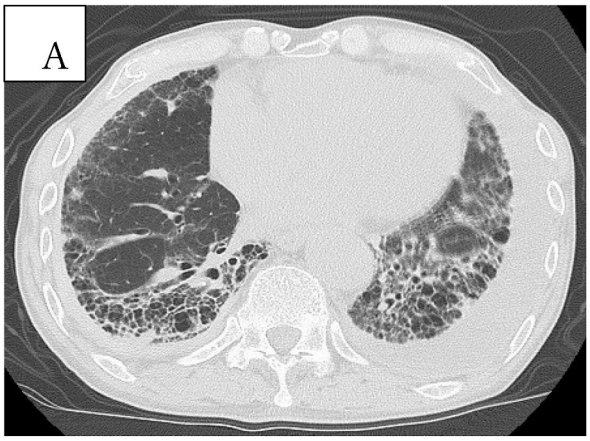

Fig. 1A. Chest computed tomography showing bronchiectasis and ground-glass opacities in bilateral lung bases, along with pleural effusion.

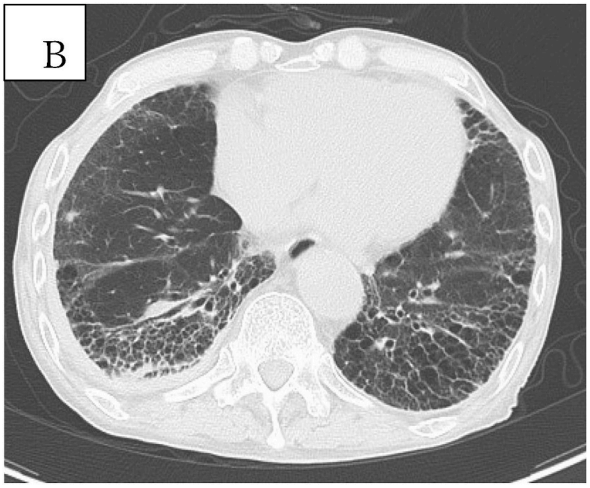

Fig. 1B. Chest computed tomography revealing the resolution of infiltrates at the bilateral lung bases and a decrease in bilateral pleural effusion.

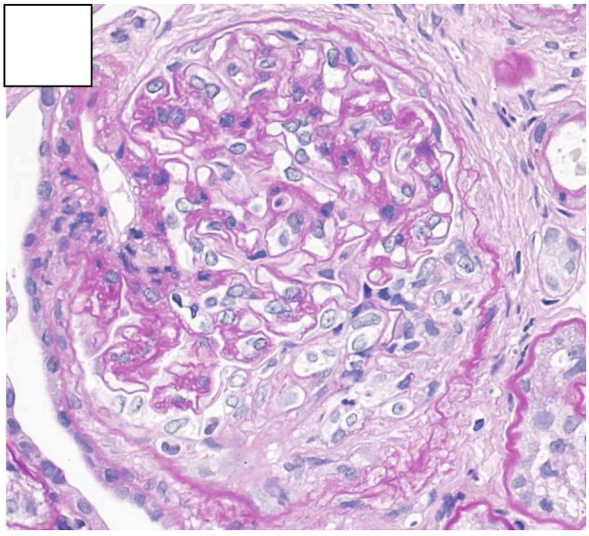

Fig. 2. Crescent formation is observed in the pathology of the renal biopsy with PAS staining.

Table 1
Changes in antibody levels.

	day-91	day1	day18	day31	day35	day57	day70
MPO-ANCA(U/mL)	5.4	163	141	62	44	14	4.3
anti-ARS antibody (index)	169	174			163		
anti-MDA-5 antibody (index)		73		37			

Day1: the day of admission.

endothelial cell damage occurs, leading to vasculitis. MDA-5, expressed on macrophage and dendritic cells, contributes to a defense mechanism that recognizes double-stranded RNA derived from viruses upon infection, related to innate immune responses [13]. It is hypothesized that SARS-CoV-2 infection triggers the production of MDA-5, followed by an abnormal autoimmune response against leaked MDA-5. It has been that 48 % of patients with COVID-19 tested positive for anti-MDA-5 antibodies. Moreover, titers of anti-MDA-5 antibody were elevated in non-survival cases. This result indicated the potential of anti-MDA-5 antibody as a prognostic marker [14]. And this immune response may lead to excessive cytokine production, NETs formation, and promotion of ANCA production in some COVID-19 patients.

In this case, in addition to MPO-ANCA, positive results were observed for anti-MDA-5 antibodies and anti-ARS antibodies. Anti-MDA-5 and anti-ARS bodies are generally mutually exclusive. There have been very few reported cases of triple positive anti-

Table 2
Previous case reports of ANCA-associated vasculitis after COVID-19 infection.

Author	Age・Sex	Positive serology	Symptom	Lung lesion	Time from COVID-19	Treatment	Outcome
Thu Aung Z et al. [2].	64・F	PR3-ANCA	hemoptysis, hemosputum	infiltative shadow	2 month later	PSL + IVCY + RTX + PE	Improvement
Ozcan S et al. [3].	26・M	MPO-ANCA	dyspnea, hemoptysis, hematuria	ground glass opacity	simultaneously	PSL + IVCY	Improvement
Giles T et al. [4].	28・M	PR3-ANCA	gastrointestinal hemorrhage	not listed	simultaneously	PSL + RTX	Improvement
Babu SS et al. [5].	59・M	PR3-ANCA	renal dysfunction	not listed	8 week later	PSL + IVCY + MMF	Improvement
Ta H et al. [6].	67・M	PR3-ANCA	dyspnea	infiltative shadow	2 week later	PSL	Improvement
Chandok T et al. [7].	57・F	MPO-ANCA	renal dysfunction	not listed	simultaneously	PSL + RTX	Improvement
Valero C et al. [8].	62・M	PR3-ANCA	peliosis	not listed	3 month later	PSL + RTX	Improvement
Mashinchi B et al. [9].	21・M	PR3-ANCA	diarrhea	not listed	simultaneously	PSL + PE	Death
Shah V et al. [10].	32・M	PR3-ANCA	eruption	patchy shadow	simultaneously	PSL	Improvement
Present case	73・M	MPO-ANCA	dyspnea	infiltative shadow, bronchiectasis	simultaneously	PSL + IVCY	Improvement

PSL: prednisolone, IVCY: intravenous cyclophosphamide, PE: plasma exchange, RTX: rituximab, MMF: Mycophenolate mofetil.

MDA5, anti-ARS antibodies and MPO-ANCA. The clinical significance of anti-ARS antibodies in this case is unclear. There has been reported cases suggesting a possible contribution of COVID-19 to the production of anti-ARS antibodies [15]. In our case, there were no changes in antibody titers following the infection or treatment. However, aminoacyl-tRNA synthetases are involved in the crucial step of generating aminoacyl-tRNAs, essential for protein synthesis. Recent research suggests they may also function as host regulatory factors in viral infections, beyond their role in protein synthesis [16] There is a possibility that aminoacyl-tRNA synthetases are involved in the replication of SARS-CoV-2 and may contribute to the onset of further cytokine storms.

In our case, SARS-CoV-2 infection may have triggered the production of NETs, which in turn led to the development of ANCA-associated vasculitis. Additionally, MDA-5 and anti-ARS antibodies may also be involved (Fig. 3).

It has been reported that SARS-CoV-2 infection can lead to autoimmune diseases such as IgG4-related diseases, rheumatoid arthritis, and systemic lupus erythematosus. This could be attributed to the occurrence of immune reactions in humans that cross-react with human proteins due to SARS-CoV-2 infection [17].

4. Limitation

NETs have not been detected in actuality. Anti-ARS antibodies have been detected before SARS-CoV-2 infection, suggesting they may not be involved in the pathogenesis. This is a case report, and further accumulation of cases is necessary.

5. Conclusion

We presented a case of MPA characterized by renal involvement and interstitial pneumonia that developed after COVID-19 infection.

In the current case, positive results for MPO-ANCA, anti-MDA-5 and anti-ARS antibodies were observed after COVID-19 infection. Elevations of these antibodies after COVID-19 infection, which may or may not cause associated disease, have been reported. Accumulation of further cases need to be accumulated in order to consider the relationship of these antibodies to COVID-19 infection or to renal involvement and interstitial pneumonia.

- After SARS-CoV-2 infection, the pathogenesis of AAV may become evident.
- There have been reports of elevated levels of anti-MDA-5 antibodies in non-survivors, indicating the significance of measuring anti-MDA-5 antibodies along with ANCA.
- Various pathologies can arise post-SARS-CoV-2 infection, necessitating the accumulation of cases for comprehensive understanding.

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CRediT authorship contribution statement

Naoto Arai: Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Toshikazu Takasaki:** Writing – original draft, Investigation, Conceptualization. **Masashi Bando:** Writing – review & editing, Supervision. **Kei Yaoita:** Writing –

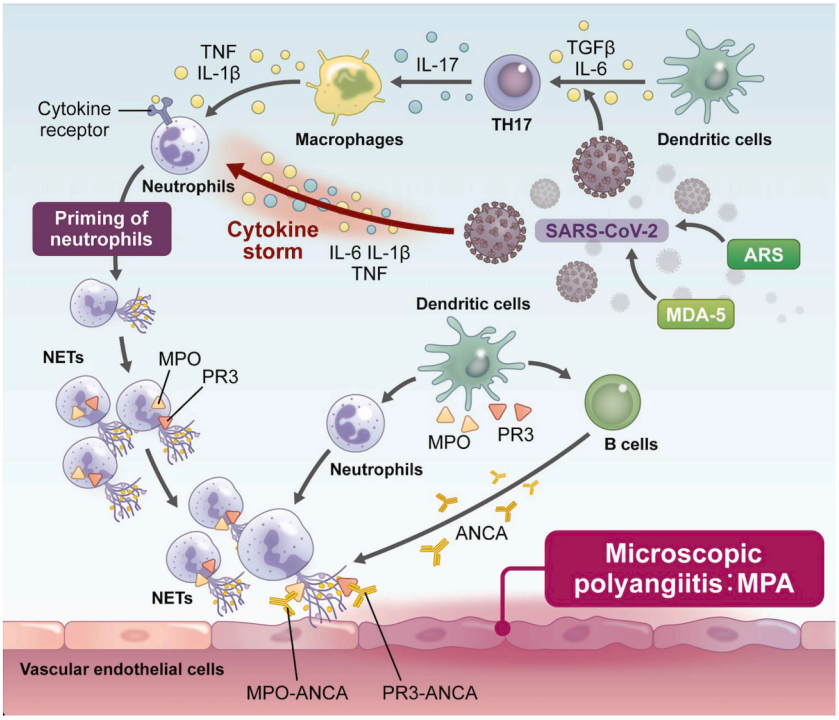

Fig. 3. Mechanism of MPA Onset Following SARS-CoV-2 Infection.
Dendritic cells recognize SARS-CoV-2 and promote the production of IL-17 by helper T cells 17. IL-17 activates macrophages, which produce inflammatory cytokines such as TNF and IL-1β, priming neutrophils. Primed neutrophils form neutrophil extracellular traps (NETs). In some patients, a cytokine storm induced by SARS-CoV-2 infection leads to excessive NET production. MDA-5 and ARS may be involved in the recognition of SARS-CoV-2 during this process. Excessive production of NETs results in loss of tolerance to self-antigens, specifically MPO and PR3. MPO and PR3 are recognized by dendritic cells, leading to further priming of neutrophils and ANCA production by B cells. Primed neutrophils express MPO and PR3 on their cell membrane to which ANCA binds. MPO-ANCA and PR3-ANCA cause damage to vascular endothelial cells, leading to the onset of vasculitis.
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review & editing. **Yutaro Ueki:** Investigation. **Shu Hisata:** Supervision. **Makoto Maemondo:** Writing – review & editing, Supervision.

Declaration of competing interest

No conflict.

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