CKJ REVIEW

ANCA-associated vasculitis flare might be provoked by COVID-19 infection: a case report and a review of the literature

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ABSTRACT

Mesangial immunoglobulin A (IgA) deposition is the hallmark of IgA nephropathy (IgAN). In some cases, crescentic involvement that might be associated with systemic leucocytoclastic vasculitis is documented. In such cases, the disease is called Henoch–Schönlein purpura (IgA vasculitis). Even more rarely, the coexistence of IgAN and anti-neutrophil cytoplasmic antibody (ANCA) seropositivity has been reported.

IgAN might be complicated by acute kidney injury (AKI) due to different causes. Herein we present a patient with mesangial IgA deposition and ANCA seropositivity who developed AKI, haematuria and haemoptysis during the course of coronavirus disease 2019 (COVID-19) disease and was diagnosed with ANCA-associated vasculitis based on clinical, laboratory and radiological findings. The patient was treated successfully with immunosuppressive therapy. We also made a systematic review of the literature to reveal and present the cases with COVID-19 and ANCA-associated vasculitis.
INTRODUCTION

Coronavirus disease 2019 (COVID-19) may trigger the development or exacerbation of autoimmune diseases [1, 2]. Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) affects small and medium-sized arteries and can progress to both kidney and lung involvement due to production of autoantibodies against the antigens myeloperoxidase (MPO) and

Table 1: Laboratory values obtained at the first admission (September 2020).

| Parameters                        | Values     | Reference range       |
|-----------------------------------|------------|-----------------------|
| Serum urea/creatinine (mg/dL)     | 37/0.99    | 17–49/0.5–0.9         |
| 24-hour urinalysis                |            |                       |
| Creatinine clearance (mL/min)     | 218        |                       |
| Total protein (mg/day)            | 3829       | ~140                  |
| Microalbumin (mg/day)             | 3330       | ~30                   |
| 24-hour urine volume (ml)         | 1850       |                       |
| Complete urinalysis               | ++         |                       |
| Protein                           | +++        |                       |
| Erythrocytes                      | 5 white blood cells, abundant red blood cells, rare squamous epithelial cells |
| Sediment                          | 4.44       | 3.5–5.2               |
| Serum albumin (g/dl)              | 13.4/39.6  | 12–16/36–48           |
| Haemoglobin (g/dl)/haematocrit (%)| 245.5      | 70–400                |
| Serum IgA (mg/dl)                 | Negative   |                       |
| ANA                               | 12.5       | ~16                   |
| Anti-dsDNA (IU/ml)                | 1.47/0.3 (normal) | 0.9–1.8/0.1–0.4     |
| C3/C4 (g/l)                       | 1.98       | Negative: <12; borderline: 12–18; positive: >18 |
| PR3-ANCA (IU/ml)                  | 173        | Negative: <12; borderline: 12–18; positive: >18 |
| MPO-ANCA (IU/ml)                  |            |                       |
Table 2: Laboratory values at the time of diagnosis of COVID-19 (January 2022) and after treatment (February 2022).

| Characteristics          | On admission | After treatment | Reference range |
|--------------------------|--------------|----------------|-----------------|
| Serum urea/creatinine (mg/dl) | 57/2.48      | 51/0.99        | 17-49/0.5-0.9   |
| Creatinine clearance (mg/dl) | NA           | 105            |                 |
| Total protein (mg/day)    | 10.456       | <140           |                 |
| Microalbumin (mg/day)     | 9687         | <30            |                 |
| 24-hour urinalysis        | 2400         |                |                 |
| Complete urinalysis       | +++          | +++            |                 |
| Protein                   | +++          | +++            |                 |
| Erythrocytes              | 10 white blood cells, abundant red blood cells, 2 squamous epithelial cells | 3 white blood cells, 27 red blood cells, 1 renal epithelial cell | |
| Serum albumin (g/dl)      | 3.48         | 3.15           | 3.5–5.2         |
| CRP (mg/l)                | 67.2         | 0.84           | <5              |
| Ferritin (ng/ml)          | 391          | 97             | 30–400          |
| D-dimer (mg/l)            | 0.94         | 0.83           | 0.4–1.4         |
| Fibrinogen (mg/dl)        | 900          | 284.5          | 180–350         |
| Haemoglobin (g/dl)        | 11.1/32.4    | 13.3/37.9      | 12–16/36–48     |
| Leucocytes (10⁹/µl)       | 7300         | 14300          | 4.3–10.3        |
| Lymphocytes (10⁹/µl)      | 800          | 2600           | 1.5–5.5         |
| ANA                       | Negative     | NA             |                 |
| Anti-dsDNA (IU/ml)        | 8.38 (negative) | NA          | <16             |
| C3/C4 (g/l)               | 1.26/0.37 (normal) | NA         | 0.9-1.8/0.1-0.4 |
| PR3-ANCA/MPO-ANCA (IU/ml) | 0.56/235 (normal/increased) | NA | Negative: <12; borderline: 12-18; positive: > 18 |

There are cases in the literature showing that COVID-19 triggers the development of AAV [4–12]. In this report we discuss a case with mesangial immunoglobulin A (IgA) deposition on kidney biopsy and ANCA seropositivity who developed acute kidney injury (AKI), haematuria and haemoptysis during COVID-19 infection and was diagnosed with AAV based on clinical, laboratory and radiological findings.

CASE PRESENTATION

A 26-year-old male patient presented to our nephrology clinic and was diagnosed with IgA nephropathy (IgAN) by renal biopsy on admission in September 2020, with 2 g/day proteinuria and haematuria. He had no history of chronic disease, smoking, alcohol, herbal substance or drug use. The kidneys sizes, echogenicity and parenchymal thickness were normal on the urinary ultrasound. The laboratory values obtained at the first admission are shown in Table 1. His anti-nuclear antibody (ANA), anti-double-stranded DNA (dsDNA) and proteinase 3 (PR3)-ANCA were negative, while his myeloperoxidase (MPO)-ANCA was positive and complement 3 (C3) and C4 were normal. The total protein in 24-hour urine was 3829 mg/day. On the kidney biopsy there were 10 glomeruli, 2 of which were global sclerotic. Light microscopic examination revealed mesangial proliferation, with no crescents and no findings related to necrotizing vasculitis. According to immunofluorescence microscopy, there was (+++) IgA deposition in the mesangium and no staining with C1q. The Oxford classification for IgAN was M1E1S1T0. Despite the high MPO levels, the patient did not have any systemic vasculitis–related findings. Secondary causes of IgA were ruled out based on the clinical and laboratory data. The patient was started on ramipril 10 mg/day. On follow-up, prednisolone 40 mg/day was started due to the increase in proteinuria (total protein in 24-hour urine, 5357 mg/day; microalbumin, 4788 mg/day). Mycophenolate mofetil was added to the treatment in April 2021, due to persistent high levels of proteinuria (4075 mg/day). However, since persistent proteinuria continued, the patient’s current immunosuppressive drug treatment was discontinued and he was accepted as unresponsive to current treatment in November 2021. The patient had two doses of Pfizer-BioNTech (BNT162b2) Comirnaty vaccine, with the last one given in June 2021.

In January 2022, the patient presented with complaints of severe progressive shortness of breath, haemoptysis, haematuria, dry cough, weakness and loss of appetite. His oxygen saturation in ambient air was 90% on admission. On auscultation, crepitant crackles were present in the mid and basal zones of the bilateral lungs. The laboratory results are presented in Table 2. The laboratory findings revealed AKI, normochromic normocytic anaemia, lymphopenia and increased C-reactive protein (CRP) and D-dimer levels. The urinalysis revealed an active sediment with haematuria and proteinuria. The patient was diagnosed with COVID-19 based on a reverse transcription polymerase chain reaction (RT-PCR) assay for SARS-CoV-2 on a nasopharyngeal swab. On chest computed tomography (CT), diffuse and predominantly peribronchovascular areas with ground glass opacity and consolidations were observed in both lung parenchymas and the findings were compatible with alveolar haemorrhage (Fig. 1). Subsequently the patient was hospitalized at the clinic for COVID-19 patients. During the follow-up, his haematocrit level decreased from 32.4% to 27.4% and his haemoglobin level decreased from 11.1 g/dl to 9.1 g/dl. The remeasured MPO-ANCA value increased to 235 IU/ml; other rheumatological markers [ANA, anti-dsDNA, rheumatoid factor, anti-cyclic citrullinated peptide, antiphospholipid syndrome antibodies, anti-Sm, anti Scl-70, anti-glomerular basement membrane...
Figure 1: Ground glass opacities in the peribronchovascular areas and consolidations.

We ran the query in March 2022 and found 102 articles in total that we manually examined. We excluded the reviews and editorials after reading the titles and abstracts. Then we read the full texts of all the articles and excluded the ones that were about COVID-19 vaccine–related AAV or those that included cases where the ANCA status was not reported or tested (Fig. 2).

The manual examination found 17 case reports describing 19 cases of AAV related to COVID-19 disease (Table 3).

**DISCUSSION**

We discussed a case that developed alveolar haemorrhage, haematuria, AKI and MPO-ANCA positivity in the course of COVID-19 and was diagnosed with AAV. There are few publications showing the development of vasculitis in patients with COVID-19 infection [4–23]. Our patient also received two doses of the messenger RNA (mRNA) COVID-19 vaccine. There are previous reports suggesting AAV flare following COVID-19 vaccine [24–27]. In most of the cases, the vaccine used was an mRNA vaccine [28]. However, in our case, the last vaccine dose was 6 months before the AAV flare. Therefore, in our patient, the temporal association favours a causal association between AAV flare and COVID-19 infection rather than an association between AAV flare and COVID-19 vaccine.

The coincidence of IgAN and AAV is a rare but previously reported condition [29–31]. It was reported that all ANCA
might not be associated with the pathology of IgAN and the classification of those overlap cases might be cumbersome. At the initial presentation, our patient did not have any systemic symptoms related to vasculitis and there was no crescentic involvement or necrotizing vasculitis on the kidney biopsy. Therefore IgA glomerulonephritis was considered in the patient with significant mesangial IgA deposition and the treatment was done accordingly. However, during the follow-up, the clinical evolution of the case suggested that the patient might be classified as renal-limited MPO-ANCA-associated vasculitis at the initial presentation.

According to our literature review, a total of 20 cases, including our case, showed an association between AAV flare and COVID-19. Obviously it is hard to infer causality based on these reports, however, a close temporal association might be considered a factor that favours causality. In 12 of the cases, COVID-19 and AVV flare were simultaneous. In the remaining eight cases, durations of 25 days to 6 months were reported (Table 3). Ten cases were male, with a median age of 46 years (range 17–86 years). Kidney biopsy was performed in 14 cases and crescentic lesions, crescentic and necrotizing lesions were observed in 6, 3 and 2 of the cases, respectively. Methylprednisolone alone or the combination of methylprednisolone with rituximab, cyclophosphamide, plasma exchange and intravenous immunoglobulin (IVIG) were the preferred treatments. Eighteen cases were alive, of which two were haemodialysis dependent, and two cases died (Table 3).

The pathogenesis of COVID-19-induced vasculitis is unclear. However, the formation of neutrophil extracellular traps (NETs) that might be triggered in COVID-19 disease was proposed as a mechanism for the development of AAV [32]. There are high levels of NETs in the circulation in patients with AAV, as shown in the kidney biopsies of these patients [33]. NETs contain pro-inflammatory proteins and are directly associated with endothelial cell damage and complement system activation. It has been suggested that PR3 and MPO contribute indirectly to the development of vasculitis through the production of ANCA. We want to point out that our patient had a high level of MPO before COVID-19 infection, which might be a predisposing factor for AAV development [34].

It is difficult to distinguish between the kidney damage that develops during the course of COVID-19 disease and the kidney damage that develops due to AAV. Many different mechanisms have been proposed that lead to the development of kidney damage in COVID-19 patients. Of them, haemodynamic factors and endothelial dysfunction lead to viral tropism in the kidney tissue, fibrinoid necrosis and microthrombosis. In addition to the direct cytopathic effects of SARS-CoV-2 on the glomeruli and renal tubules, indirect effects such as cellular immunity and cytokine storm play a role in kidney damage [11]. Unfortunately, we did not perform a second kidney biopsy during the flare. Therefore we cannot reveal the exact cause of kidney damage in our patient. There are some other limitations in this current report, e.g. the patient was referred from a different centre. Therefore we do not have the results of CRP, ESR, cryoglobulin anti-GBM at the first presentation and electron microscopic examination was not performed in the kidney biopsy. Moreover, MPO titre after treatment is not available.

Considering the severity of the patient’s pulmonary AAV, cyclophosphamide was administered together with glucocorticoid therapy as the standard treatment, and the patient responded dramatically. Despite the presence of COVID-19 infection, as observed in similar cases in the literature, our patient also had a good response to immunosuppressive therapy.

In conclusion, COVID-19 might trigger a vasculitis flare, especially in patients with predisposing factors. It should be kept in mind that AAV should be included in the differential diagnosis in patients with COVID-19 who present with AKI and pulmonary involvement.
| Reference          | Country                        | Age (years) | Gender | Time between COVID-19 and AAV | Serology | Lung involvement                  | Renal biopsy          | Treatment                                                                 | Outcome  |
|--------------------|--------------------------------|-------------|--------|------------------------------|----------|-----------------------------------|-----------------------|---------------------------------------------------------------------------|----------|
| Moeinzadeh et al.  | Iran                           | 25          | Male   | Simultaneous                 | c-ANCA   | Alveolar haemorrhage              | Crescent GN           | Methylprednisolone + plasma exchange, cyclophosphamide                    | Living   |
| Uppal et al. [5]   | USA (African American)         | 64          | Male   | Simultaneous                 | MPO (p-ANCA) | Bilateral patchy infiltrates     | Crescent GN           | Methylprednisolone + rituximab                                           | Living   |
| Uppal et al. [5]   | USA (South Asian)              | 46          | Male   | Simultaneous                 | PR3 (c-ANCA) | Resolving peripheral ground glass opacities | Focal necrotizing GN | Methylprednisolone + rituximab                                           | Living   |
| Hussein et al. [6] | Saudi Arabia                   | 37          | Female | Simultaneous                 | PR3 (c-ANCA) | Alveolar haemorrhage              | No, AKI               | Methylprednisolone + plasma exchange, IVIG                              | Died     |
| Jalalzadeh et al.  | USA (Hispanic)                 | 46          | Female | 6 months                     | MPO (p-ANCA) | Bilateral pleural effusions and pulmonary infiltrates | Crescent GN, pauci-immune | Methylprednisolone                                                      | Living   |
| Selvamaj et al. [14]| USA                           | 60          | Female | 4 weeks                      | PR3 (c-ANCA) | Alveolar haemorrhage              | Crescent and necrotizing GN, TIN          | Methylprednisolone + plasma exchange, rituximab                     | Living   |
| Izci Duran et al.  | Turkey                         | 26          | Male   | Simultaneous                 | MPO (p-ANCA) | Subpleural and parenchymal dispersed consolidative ground glass opacities | Crescent GN           | Methylprednisolone + cyclophosphamide, plasma exchange                   | Living, HD dependent |
| Izci Duran et al.  | Turkey                         | 36          | Female | Simultaneous                 | PR3 (c-ANCA) | Bilateral cavitary lesions        | Necrotizing crescentic GN | Methylprednisolone + cyclophosphamide                                  | Living   |
| Lind et al. [15]   | USA                            | 40          | Male   | 5 weeks                      | PR3 (c-ANCA) | Alveolar haemorrhage              | Focal crescentic GN    | Methylprednisolone + rituximab                                           | Living   |
| Allena et al. [9]  | USA                            | 60          | Female | Simultaneous                 | MPO (p-ANCA) | Alveolar haemorrhage              | Focal segmental necrotizing, crescentic and sclerosing GN, pauci-immune type | Methylprednisolone + plasma exchange, rituximab                     | Living   |
| Reference          | Country       | Age (years) | Gender | Time between COVID-19 and AAV | Serology     | Lung involvement                        | Renal biopsy                  | Treatment                                                                 | Outcome     |
|--------------------|---------------|-------------|--------|-------------------------------|--------------|-----------------------------------------|------------------------------|----------------------------------------------------------------------------|-------------|
| Reiff et al. [16]  | USA           | 17          | Male   | Simultaneous                  | PR3 (c-ANCA) | Pulmonary nodules                       | No, normal kidney function  | Methylprednisolone + rituximab                                          | Living      |
| Maritati et al. [10]| Italy         | 64          | Female | Simultaneous                  | PR3 (c-ANCA) | Bilateral interstitial pneumonia with ground glass opacities | Pauci-immune GN | Methylprednisolone + plasma exchange, cyclophosphamide | Living      |
| Fineizen et al. [17]| USA           | 17          | Male   | 2 months                      | MPO (p-ANCA) | Alveolar haemorrhage                    | Necrotizing GN with limited immune complex deposition | Methylprednisolone + cyclophosphamide | Living      |
| Cobilinschi et al. [18]| Romania      | 67          | Female | Simultaneous                  | p-ANCA       | No                                       | No, AKI                      | Methylprednisolone + cyclophosphamide | Living      |
| Morris et al. [19] | USA (Hispanic)| 53          | Male   | 1 month                       | PR3 (c-ANCA), MPO ANCA (mildly +) | Multifocal pneumonia, alveolar haemorrhage | No, AKI                      | Methylprednisolone + cyclophosphamide | Died        |
| Kawashima et al. [20]| Japan        | 61          | Female | 3 months                      | MPO (p-ANCA) | No                                       | Highly active nephritis associated with AAV | Methylprednisolone + cyclophosphamide | Living      |
| Felzer et al. [21] | USA           | 86          | Female | Simultaneous                  | MPO (p-ANCA) | Alveolar haemorrhage                    | No, AKI                      | Methylprednisolone + rituximab                                          | Living      |
| Wali et al. [22]   | USA           | 26          | Female | 25 days                       | MPO (p-ANCA) | Alveolar haemorrhage                    | GN associated with AAV Pauci-immune fibrocellular crescentic GN on top of glomerular sclerosis | Methylprednisolone + cyclophosphamide | Living      |
| Madanchi et al. [23]| USA           | 53          | Male   | 4 months                      | MPO (p-ANCA) | Alveolar haemorrhage                    | No, AKI                      | Methylprednisolone + cyclophosphamide | Living, HD dependent |
| Current case       | Turkey        | 26          | Male   | Simultaneous                  | MPO (p-ANCA) | Alveolar haemorrhage                    | No, AKI                      | Methylprednisolone + cyclophosphamide | Living      |

c-ANCA: cytoplasmic ANCA; GN: glomerulonephritis; p-ANCA: perinuclear ANCA; TIN: tubulointerstitial nephritis.
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The present work was conducted in accordance with the Declaration of Helsinki.
Informed consent was obtained from the patient for publication of this case report and accompanying images.

DATA AVAILABILITY STATEMENT
All data generated or analysed during this study are included in this article.

CONFLICT OF INTEREST STATEMENT
The authors have no conflicts of interest to declare.

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