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

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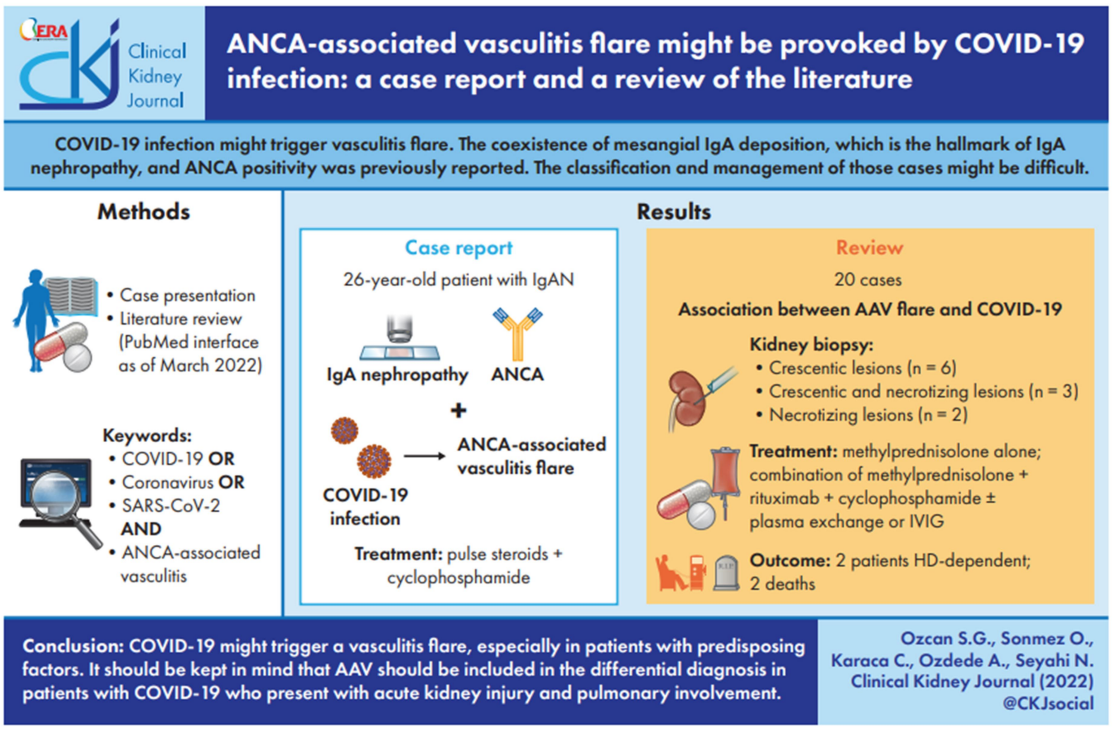
GRAPHICAL ABSTRACT



ABSTRACT

Mesangial IgA deposition is the hallmark of IgA nephropathy. In some cases, crescentic involvement which might be associated with systemic leukocytoclastic vasculitis is documented; in such cases, the disease is called Henoch-Schonlein purpura (IgA vasculitis). Even more rarely, the coexistence of IgA nephropathy and ANCA seropositivity was reported.

IgA nephropathy might be complicated by acute kidney injury due to different causes. Herein, we present a patient with mesangial IgA deposition and ANCA seropositivity, who developed acute kidney injury, hematuria, and hemoptysis during the course of COVID-19 disease and was diagnosed with anti-neutrophil cytoplasmic antibody (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.

Keywords: ANCA, ANCA associated vasculitis , COVID-19, IgA nephropathy, vasculitis

INTRODUCTION

The coronavirus disease (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 proteinase 3 (PR3). (3) 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 IgA deposition in kidney biopsy and ANCA seropositivity, who developed acute kidney injury, hematuria, and hemoptysis during COVID-19 infection and was diagnosed with AAV based on clinical, laboratory, and radiological findings.

CASE PRESENTATION

A 26-year-old male patient applied to our nephrology clinic and was diagnosed with IgA nephropathy by renal biopsy on admission in September 2020, with 2 grams/day proteinuria and hematuria. He had no history of chronic disease, smoking, alcohol, herbal substance, or drug use. The kidney 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 ANA, anti-dsDNA, and PR3-ANCA were negative, while his MPO-ANCA was positive and C3 and C4 were normal. The total protein in 24-hour urine was 3829 mg/day. In the kidney biopsy there were 10 glomeruli, two 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 IgA nephropathy 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. In the 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 shots of Pfizer BioNTech (BNT162b2) Comirnaty vaccine, the last one of which was given in June 2021.

In January 2022, the patient presented with complaints of severe progressive shortness of breath, hemoptysis, hematuria, 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 acute kidney injury (AKI), normochromic normocytic anemia, lymphopenia, and increased C-reactive protein (CRP) and D-dimer levels. The urinalysis revealed an active sediment with hematuria and proteinuria. The patient was diagnosed with COVID-19 based on the 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 hemorrhage (Figure 1). Subsequently, the patient was hospitalized at the clinic for COVID-19 patients. During the follow-up, his hematocrit level decreased from 32.4% to 27.4%; hemoglobin level decreased from 11.1 g/dl to 9.1 g/dl. The re-measured MPO-ANCA value increased to 235 IU/ml; other rheumatological markers (ANA, anti-dsDNA, RF, anti-CCP, antiphospholipid syndrome antibodies, anti-Sm, anti Scl-70, anti-GBM) were negative. Increased MPO-ANCA level, AKI, alveolar hemorrhage, and

chest CT findings led to the diagnosis of AAV. Therefore, 1000 mg of intravenous methylprednisolone daily was administered for three days, which led to remarkable symptomatic improvement in oxygen saturation levels. After pulse steroid treatment, the decrease in the hematocrit level stopped, and complaints of hemoptysis and hematuria were significantly reduced. Then, prednisolone 1 mg/kg/day was initiated. In addition, cyclophosphamide administration 1000 mg/month was planned. Post-treatment laboratory values are shown in Table 2.

LITERATURE REVIEW

The presence of COVID-19 and AAV in the same patient might be a co-incidence, however, the presence of similar previous cases might favor an association. Therefore, we made a review of the literature.

We used the PubMed interface (pubmed.gov) to make a query using the combination of the following two keyword groups. The first group included the keywords "COVID-19", "coronavirus", "SARS-CoV-2" and the second group included the keyword "ANCA-associated vasculitis". Each keyword in the same group was combined using the logical operator "OR", while the two groups were combined using the logical operator "AND". We excluded the reviews, editorials, and case reports which were about COVID vaccine-related AAV.

We ran the query in March 2022. In return, we found 102 articles in total and we manually examined them. We excluded the reviews and editorials after reading the titles and abstracts. Then, we read all the articles' full texts and excluded the ones that were about COVID-19 vaccine-related AAV, or those that included cases whose ANCA statuses were not reported or tested (Figure 2).

After the manual examination, we found 17 case reports describing 19 cases about AAV related to COVID-19 disease (Table 3).

DISCUSSION

We discussed a case that developed alveolar hemorrhage, hematuria, 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 m-RNA 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 m-RNA vaccine. (28) However, in our case, the last dose of

vaccination was six months before the AAV flare. Therefore, in our patient, the temporal association favors a causal association between AAV flare and COVID-19 infection rather than an association between AAV flare and COVID-19 vaccine.

The coincidence of IgA nephropathy and AAV is a rare but previously reported condition (29-31). It was reported that all ANCAs might not be associated with the pathology of IgA nephropathy 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 in 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 those reports, however, a close temporal association might be considered as a factor that favors causality. In 12 of the cases, COVID-19 and AVV flare were simultaneous. In the remaining eight cases, a duration between 25 days to 6 months were reported (Table 3). Ten cases were male, with a median age of 46 years (range: 17 to 86 years). Kidney biopsy was performed in 14 cases and crescentic lesions, crescentic and necrotizing lesions, and necrotizing lesions were observed in six, three, and two of the cases respectively. Methylprednisolone alone or the combination of methylprednisolone with rituximab, cyclophosphamide, plasma exchange and IVIG were the preferred treatments. Eighteen cases were alive, of which two were hemodialysis dependent, and two cases were dead (Table 3).

The pathogenesis of COVID-19-induced vasculitis is not clear. 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 proinflammatory 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, hemodynamic 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; the patient was referred from a different center. 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 titer 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.

STATEMENT OF ETHICS

The present work was conducted in accordance with the Declaration of Helsinki.

CONSENT TO PUBLISH STATEMENT

Informed consent was obtained from the patient for publication of this case report and accompanying images.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this article.

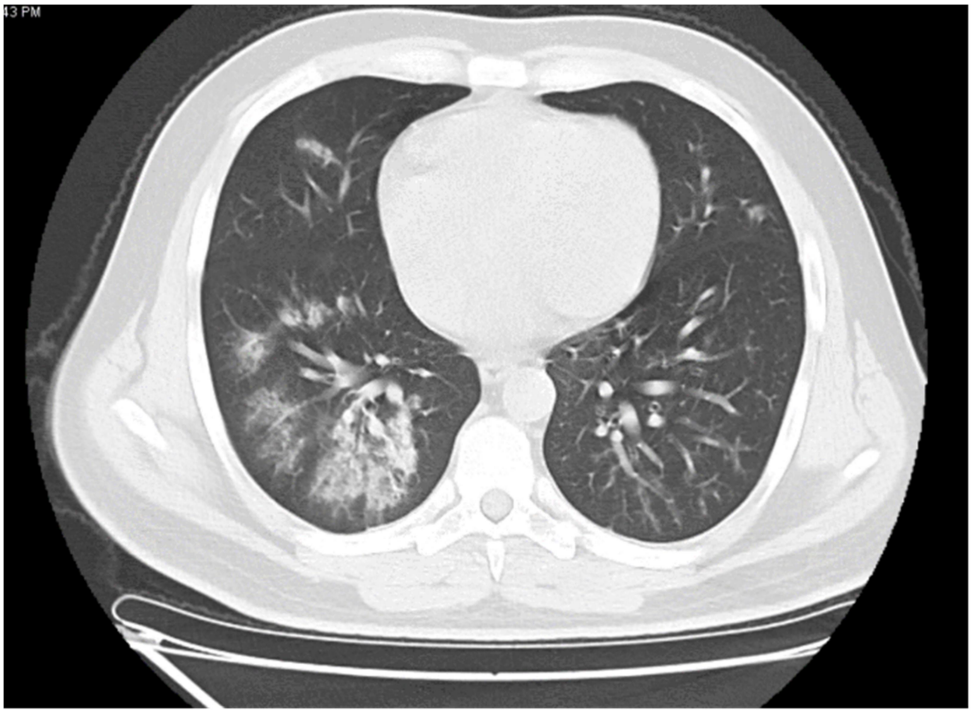


Figure 1. Ground-glass opacities in peribronchovascular areas and consolidations.

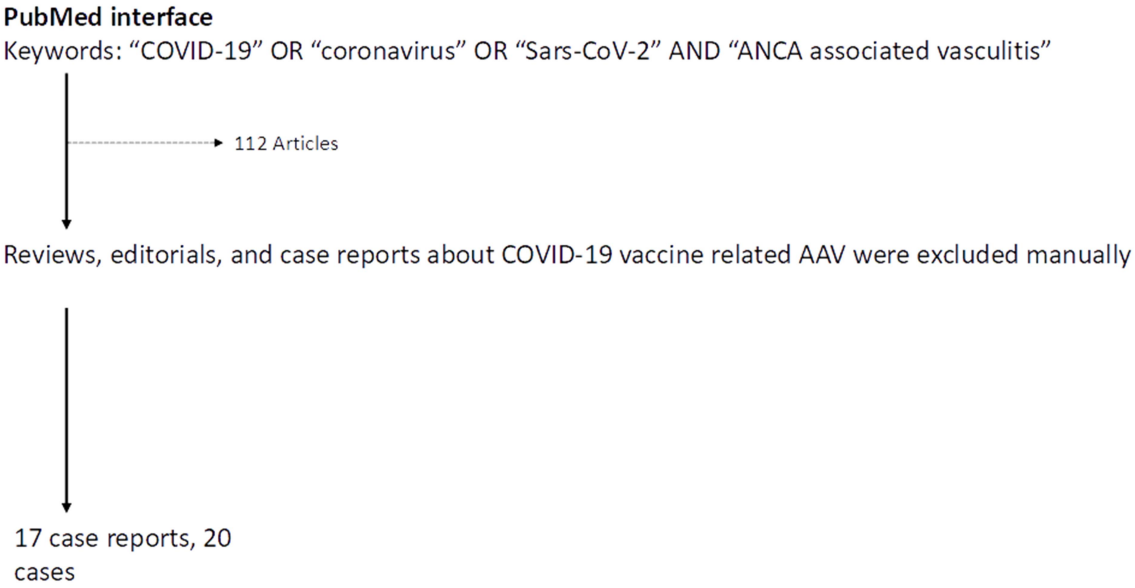


Figure 2. Steps of the literature review.

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Table 1. Laboratory values obtained at the first admission (Sep, 2020)

Parameters	Values	Reference range
Serum urea/creatinine (mg/dL)	37/0.99	17-49/0.5-0.9
24 h urine analysis Creatinine clearance (ml/min) Total protein (mg/day) Microalbumin (mg/day) 24 h urine volume (mL)	 218 3829 3330 1850	 <140 <30
Complete urine analysis Protein Erythrocyte Sediment	 ++ +++ 5 WBC, abundant RBC, rare squamous epithelial cells	
Serum albumin (g/dL)	4.44	3.5-5.2
Hemoglobin (g/dL) / Hematocrit (%)	13.4/39.6	12-16/36-48
Serum IgA (mg/dL)	245.5	70-400
ANA	negative	
Anti-dsDNA (IU/mL)	12.5	<16
C3/C4 (g/L)	1.47/0.3 (normal)	0.9-1.8/0.1-0.4
PR3-ANCA (IU/mL)	1.98	Negative: <12, borderline: 12-18, positive: >18
MPO ANCA (IU/mL)	173	Negative: <12, borderline: 12-18, positive: >18

H: hour IgA: immunoglobulin A, ANA: anti-nuclear antibody, Anti-dsDNA: anti-double stranded DNA antibody, PR3: proteinase 3, MPO: myeloperoxidase, C3: complement 3, C4: complement 4.

Table 2. Laboratory values at the time of diagnosis of COVID-19 (Jan, 2022) and after treatment (Feb, 2022)

	On admission	After treatment	Reference range
Serum urea/creatinine (mg/dL)	57/2.48	51/0.99	17-49/0.5-0.9
24 h urine analysis Creatinine clearance (ml/min) Total protein (mg/day) Microalbumin (mg/day) 24 h urine volume (mL)	NA	105 10456 9687 2400	<140 <30
Complete urine analysis Protein Erythrocyte Sediment	+++ +++ 10 WBC, abundant RBC, 2 squamous epithelial cells	+++ +++ 3 WBC, 27 RBC, 1 renal epithelial cell	
Serum albumin (gr/dL)	3.48	3.15	3.5- 5.2
C-reactive protein (mg/L)	67.2	0.84	<5
Ferritin (ng/mL)	391	97	30-400
D-dimer (mg/L)	0.94	0.83	0-0.5
Fibrinogen (mg/dL)	900	284,5	180-350
Hemoglobin (gr/dL) / Hematocrit (%)	11.1/32.4	13.3/37.9	12-16/36-48
Leucocyte (10^3 /µl)	7300	14300	4.3-10.3
Lymphocyte (10^3 /µl)	800	2600	1.5-3.5
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

H: hour IgA: immunoglobulin A, ANA: anti-nuclear antibody, Anti-dsDNA: anti-double stranded DNA antibody, PR3: proteinase 3, MPO: myeloperoxidase, C3: complement 3, C4: complement 4.

Table 3. Review of the COVID-19-related AAV cases (sorted by the release date from oldest to newest)

Reference no	Country	Age	Gender	Duration between COVID-19 and AAV	Serology	Lung involvement	Renal biopsy	Treatment	Outcome
(11)	Iran	25	Male	Simultaneous	c-ANCA	Alveolar hemorrhage	Crescentic GN	Methylprednisolone + plasma exchange, cyclophosphamide	Living
(5)	USA (African American)	64	Male	Simultaneous	MPO (p-ANCA)	Bilateral patchy infiltrates	Crescentic GN	Methylprednisolone + rituximab	Living
(5)	USA (South Asian)	46	Male	Simultaneous	PR3 (c-ANCA)	Resolving peripheral ground glass opacities	Focal necrotizing DN	Methylprednisolone + rituximab	Living
(6)	Saudi Arabia	37	Female	Simultaneous	PR3 (c-ANCA)	Alveolar hemorrhage	No, AKI	Methylprednisolone + plasma exchange, IVIG	Exitus
(13)	USA (Hispanic)	46	Female	6 months	MPO (p-ANCA)	Bilateral pleural effusions and pulmonary infiltrates	crescentic GN, pauci immune	Methylprednisolone	Living
(14)	USA	60	Female	4 weeks	PR3 (c-ANCA)	Alveolar hemorrhage	crescentic and necrotizing GN, TIN	Methylprednisolone + plasma exchange, rituximab	Living
(7)	Turkey	26	Male	Simultaneous	MPO (p-ANCA)	Subpleural and parenchymal dispersed consolidative ground-glass opacities	Crescentic GN	Methylprednisolone + cyclophosphamide, plasma exchange	Living, HD dependent
(7)	Turkey	36	Female	Simultaneous	PR3 (c-ANCA)	Bilateral cavitary lesions	Necrotizing crescentic GN	Methylprednisolone + cyclophosphamide	Living
(15)	USA	40	Male	5 weeks	PR3 (c-ANCA)	Alveolar hemorrhage	focal crescentic GN	Methylprednisolone + rituximab	Living
(9)	USA	60	Female	Simultaneous	MPO (p-ANCA)	Alveolar hemorrhage	focal segmental necrotizing, crescentic and sclerosing GN, pauci-immune type	Methylprednisolone + plasma exchange, rituximab	Living
(16)	USA	17	Male	Simultaneous	PR3 (c-ANCA)	Pulmonary nodules	No, normal kidney function	Methylprednisolone + rituximab	Living
(10)	Italy	64	Female	Simultaneous	PR3 (c-ANCA)	bilateral interstitial pneumonia with ground-glass	Pauci-immune GN	Methylprednisolone + plasma exchange, cyclophosphamide	Living

						opacities			
(17)	USA	17	Male	2 months	MPO (p-ANCA)	Alveolar hemorrhage	necrotizing GN with limited immune complex deposition.	Methylprednisolone + cyclophosphamide	Living
(18)	Romania	67	Female	Simultaneous	p-ANCA	No	No, AKI	Methylprednisolone + cyclophosphamide	Living
(19)	USA(Hispanic)	53	Male	1 month	PR3 (c-ANCA), MPO ANCA (mildly +)	Multifocal pneumonia, alveolar hemorrhage	No, AKI	Methylprednisolone	Exitus
(20)	Japan	61	Female	3 months	MPO (p-ANCA)	No	highly active nephritis associated with AAV	Methylprednisolone + cyclophosphamide	Living
(21)	USA	86	Female	Simultaneous	MPO (p-ANCA)	Alveolar hemorrhage	No, AKI	Methylprednisolone + rituximab	Living
(22)	USA	26	Female	25 days	p-ANCA	Alveolar hemorrhage	glomerulonephritis associated with AAV	Methylprednisolone + rituximab	Living
(23)	USA	53	Male	4 months	MPO (p-ANCA)	Alveolar hemorrhage	pauci-immune fibro-cellular crescentic GN on top of glomerular sclerosis	Methylprednisolone + cyclophosphamide	Living, HD dependent
Current Case	Turkey	26	Male	Simultaneous	MPO (p-ANCA)	Alveolar hemorrhage	No, AKI	Methylprednisolone + cyclophosphamide	Living

PR3: proteinase 3, MPO: myeloperoxidase, AKI: acute kidney injury, ANCA: anti-neutrophil cytoplasmic antibody, GN: glomerulonephritis, TIN: tubulointerstitial nephritis.