



# Challenges of Diagnosis and Treatment of ANCA Associated Vasculitis in COVID-19 Pandemic - A Case Report

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## ABSTRACT

As COVID-19 pandemic is spreading worldwide with high infectivity rates of various strains, it is also challenging our healthcare system with its respiratory complications, and limited availability of healthcare providers. On the other hand, a huge vaccination program against COVID-19 is being conducted throughout the world. This viral infection and vaccination program has also brought into account the controversies of some neurological and autoimmune complications. Although the exact mechanism of these complications is still unknown, some autoimmune mechanisms have been predicted. These complications may further challenge the management of this novel viral infection. One of the rare complications of COVID-19 infection and its vaccination is de novo development or flare of ANCA-associated vasculitis, which has also been found in many recent case reports.

**Keywords:** Covid-19, Vasculitis, Granulomatosis with Polyangitis



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## INTRODUCTION:

ANCA associated vasculitis (AAV) is a group of autoimmune diseases primarily affecting small vessels. Granulomatosis with polyangitis (GPA) is a type of AAV in which necrotizing granulomatous inflammation of upper and lower respiratory tract, vasculitis of small to medium vessels, and glomerulonephritis can be seen. Typical features of GPA include nasal crusting, stiffness and epistaxis, pain in multiple joints, uveitis, upper and lower respiratory tract involvement and renal involvement<sup>1</sup>. More than 90% of those suffering from GPA with multisystem involvement have C-ANCA positivity<sup>2</sup>.

The novel coronavirus disease 2019 (COVID-19) pandemic has challenged our healthcare system in various ways, be it the hospital admission availability, respiratory complications of a viral infection, or increase in incidence rate of many autoimmune diseases. This has also initiated the largest vaccination program in history. Novel vaccines containing messenger ribonucleic acid (mRNA) or a viral deoxyribonucleic acid (DNA) vector with spike glycoprotein have already been approved. Large clinical trials have shown that these COVID-19 vaccines are safe and effective. Common adverse events include mild to moderate reactions at the injection site, fever, fatigue, body aches, and headache<sup>3</sup>. Both COVID-19 infection and vaccination against it have been found to be associated with the development or relapse of many autoimmune diseases including AAV<sup>4,5</sup>. We hereby present a case of AAV one month after vaccination with first dose of ChAdOx1 vaccine.

## CASE REPORT:

A 32-year-old female from Kathmandu, Nepal presented in Department of Internal Medicine, KIST Medical College Teaching Hospital with blood mixed sputum for five days, fever and acute shortness of breath for two days. She was diagnosed

as seronegative rheumatoid arthritis one year back on the basis of history of pain in multiple joints, clinical examination, and raised inflammatory markers. She was then put on oral Methotrexate 10 mg weekly with partial improvement of symptoms, which she took regularly for two months and then stopped due to gastrointestinal intolerance. She has a history of pain in multiple joints for one year, an episode of hemoptysis one year back, which persisted for three days, and recurrent nasal bleeding. She had received ChAdOx1 vaccine one month back. On examination, she was tachypneic with respiratory rate of 24/minute, oxygen saturation was 83% without oxygen supplement, blisters of multiple sizes and shapes were present in bilateral (B/L) fingers and foot, and hyperpigmented macules and patches of variable sizes were present in B/L upper and lower limbs. Chest examination revealed B/L crepitation, and musculoskeletal examination revealed tenderness in B/L metacarpophalangeal and knee joints. She was then admitted in intensive care unit with some antibiotics and fluid support. Her chest radiography showed B/L patchy opacities occupying all lung fields [Figure 1] consistent with COVID-19 pneumonia, and her HRCT chest showed ground glass opacities in B/L lung fields [Figure 2]. Other investigation reports are shown in Table 1.

On the third day of admission, she started developing splinter hemorrhages on nail beds of B/L hands. On the basis of these findings, provisional diagnosis of ANCA associated vasculitis (AAV) with possible diffuse alveolar hemorrhage was made. Injection Methylprednisolone was started at 1gram per day for three days. Bluish to dark reddish discoloration of right little finger started appearing from 4th day, which gradually

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progressed to dry gangrene formation [Figure 3]. On 5th day of admission, patient had worsening of respiratory symptoms and oxygen saturation fell down to 75% at oxygen supplement of 15L/min via Venturi mask. Patient was then electively intubated, and put in ventilator support. Injection Methylprednisolone was followed by administration of Injection Cyclophosphamide according 1 gram intravenously was started, and continued for 3 consecutive days, followed by injection cyclophosphamide according to CYCLOPS protocol<sup>6</sup>. In the meantime, echocardiography revealed acute intra-ventricular thrombus, for which anticoagulation was started.

After five days of intubation and ventilator support, she was fit to be extubated. The dry gangrene was further evaluated and no active intervention was done. After one month of hospital stay, she was discharged on oral prednisolone 1mg/kg/day with plan of further tapering, calcium carbonate and vitamin D3 supplements. Intravenous cyclophosphamide was continued according to CYCLOPS protocol<sup>6</sup>.

C-ANCA	Positive by Immunofluorescence microscopy
P-ANCA	Negative
C3	129.7 mg/dL (Ref. 90-180)
C4	21.7 mg/dL (Ref. 10-40)
Influenza RT-PCR	Positive
Chest X-ray	B/L patchy opacities
High resolution CT-scan of chest	Ground glass opacities occupying B/L lung fields
CT pulmonary angiogram	Normal

**Table 1: Laboratory and radiographic investigations**

Investigations	Reports
Hemoglobin	8.1 mg/L
WBC	5200/cumm
ESR	90 mm in 1st hour
CRP	126
Renal Function Test	Within normal limits
Liver Function Test	Within normal limits
Urine microscopy	Within normal limits
D-dimer	>10 mg/L
Ferritin	139.2 ng/mL
Procalcitonin	0.19 ng/ml
RT PCR for COVID-19	Negative
SARS-COV-2 spike IGG antibodies	4484.60 (Ref. <50)
Rheumatoid Factor	Negative
Anti Citrullinated Peptide antibody	<7.0 U/mL (Negative)
Anti Nuclear Antibody (ANA)	Negative

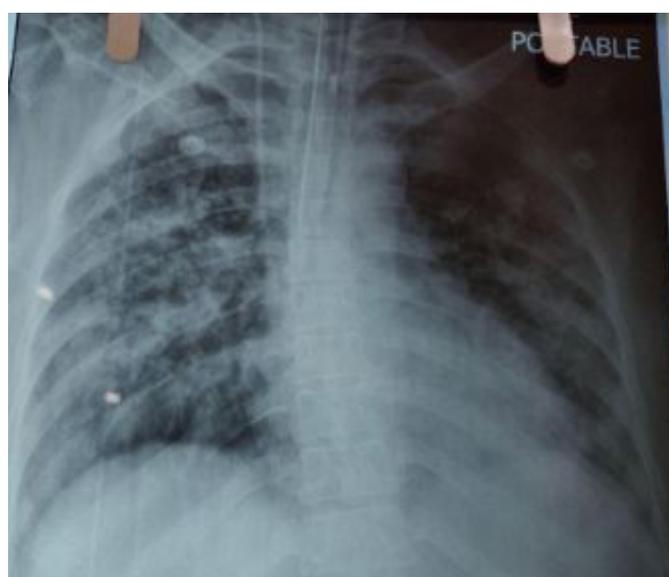


Figure 1

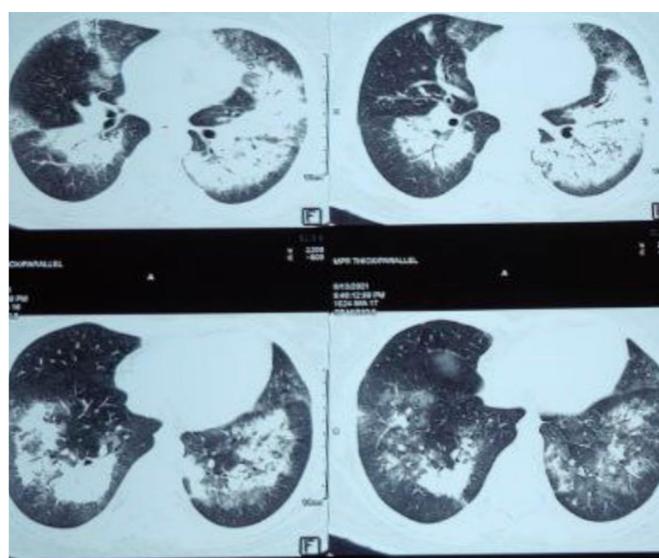


Figure 2



Figure 3

### DISCUSSION:

Recent studies and case reports have shown evidence of de novo development and relapse of AAV after COVID 19 infection as well as post-COVID vaccination<sup>5,7,8</sup>. Influenza vaccine has also been associated with autoimmune illnesses including leukocytoclastic vasculitis, Henoch-Schönlein purpura, giant cell arteritis and AAV in predisposed individuals with pre-existing autoimmune diseases<sup>5</sup>. A few cases of AAV following COVID-19 vaccination are being reported in the literature following BNT162b29,<sup>10</sup> ChAdOx1<sup>11</sup>, and mRNA-1273 vaccine<sup>12,13</sup>.

One of the possibilities in this case could be diffuse alveolar hemorrhage (DAH), as hemoptysis with moderate amount of blood loss was present. DAH can be seen both in COVID-19 pneumonia and GPA. A study has shown that the incidence of DAH in AAV ranges from 8 to 36%, with 41% of these diagnosed as GPA<sup>14</sup>. Few case reports have also shown findings of DAH in COVID pneumonia<sup>15,16</sup>. For further workup, she had been planned for bronchoscopy, but due to rapid presentation of gangrene and respiratory failure, we had to intervene immediately. Another finding in this case was presence of intra-ventricular thrombus. Risk of thromboembolic event is also common in GPA. A higher incidence of thromboembolic events has been associated with AAV<sup>17,18</sup>. To rule out SARS cov-2 infection, we conducted PCR, which was negative, but COVID antibodies were high.

The exact pathophysiology is still unknown. One of the possibilities could be enhanced immune response after COVID-19 vaccination, which is responsible for triggering the ANCA ultimately leading to AAV. Molecular mimicry and cross-reactivity have been considered as a trigger for auto-inflammatory diseases<sup>19</sup>. COVID-19 patients were also found to be at a higher risk of developing autoimmune diseases including systemic lupus erythematosus, Guillain-Barre syndrome, and Kawasaki disease<sup>20</sup>. Several cases of AAV occurring in patients with COVID-19 have been described<sup>20,21</sup>, supporting the hypothesis that the virus itself, or the immune

response to it, could trigger the development of ANCA, leading to AAV. Future immunological and case studies might be helpful for establishment of robust mechanism and guidance of treatment in this kind of scenario.

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