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Case Report PEDIATRICS

A pediatric case of Takayasu's arteritis with anti-neutrophil cytoplasmic antibody-associated vasculitis triggered by COVID-19 infection

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ABSTRACT

Takayasu's arteritis (TA) is a rare chronic granulomatous vasculitis characterized by large-vessel involvement. The aorta and its main branches are most commonly involved. Although pulmonary artery involvement is common, hemoptysis or respiratory findings are rarely seen. Herein, we present a case of TA who developed anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis with diffuse alveolar hemorrhage after coronavirus disease 2019 (COVID-19) infection. A 17-year-old female patient with the diagnosis of TA presented with cough, bloody vomiting, and diarrhea. In follow-up, she developed tachypnea and dyspnea and was transferred to the pediatric intensive care unit. The findings on the chest computed tomography were compatible with acute COVID-19 infection, but the SARS-CoV2 reverse transcription-polymerase chain reaction test was negative, but SARS-CoV2 immunoglobulin (Ig) G and IgM antibody tests were positive. The patient was not vaccinated against COVID-19. The bronchoscopy showed bronchial mucosal fragility, bleeding foci, and mucosal bleeding. The broncoalveolar lavage hemosiderin-laden macrophages were seen in the histopathologic examination. The indirect immunofluorescence assay-ANCA test became 3 (+) with myeloperoxidase (MPO)-ANCA of 125 RU/ml (normal: <20). Cyclophosphamide and pulse steroid treatment were started. After immunosuppressive therapy, the patient condition improved and did not have hemoptysis again. The successful response was obtained by applying balloon angioplasty to the patient with bilateral renal artery stenosis. Types of post-COVID vasculitis include thromboembolic events, cutaneous vasculitis, Kawasaki-like vasculitis, myopericarditis, and ANCA-associated vasculitis. It is thought that COVID-19 may impair immune tolerance and trigger autoimmunity with cross-reaction. To the best of our knowledge, the third pediatric case was reported with MPO-ANCA-positive COVID-associated ANCA vasculitis.

Keywords: Anti-neutrophil cytoplasmic antibody-associated vasculitis; coronavirus disease 2019; rheumatology; Takayasu's arteritis.

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Takayasu's arteritis (TA) is a rare chronic granulomatous vasculitis characterized by large-vessel involvement. The aorta and its main branches are most commonly involved. Although it is more common in adolescents, it can also be seen in younger ages, including the 1st year of life [1]. Although the variability of the clinical findings depends on the stage of the disease and the vascular involvement pattern, the most common

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clinical findings are the triad of constitutional symptoms, hypertension, and high acute phase response. Although pulmonary artery involvement is common, hemoptysis or respiratory findings are rarely seen [2].

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis is a necrotizing vasculitis characterized by small vessel involvement. Epidemiological data in childhood are limited. It is more common in females than males. At diagnosis, the mean age has been reported as 10–14 years old [3]. According to the clinicopathological classification, it is called granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). In recent years, the classification has been modified according to the ANCA pattern seen in immunofluorescence microscopy. According to this new classification, proteinase 3 (PR3) ANCA is defined as the cytoplasmic pattern and has been particularly associated with GPA (60%–80%). Myeloperoxidase (MPO) ANCA is defined as the perinuclear pattern and is frequently associated with MPA (80%–90%) and lesser with EGPA (35%–40%) [4]. Differences in genetics, pathogenesis, risk factors, and treatment responses were more closely related to PR3 or MPO-ANCA type than clinicopathological classification [4]. Ear, nose, sinus, and throat involvement is more common in PR3-ANCA patients. Lung involvement is seen in both PR3-ANCA and MPO-ANCA patients, while interstitial lung disease is more common in MPO-ANCA patients. Renal involvement is also observed more frequently in MPO-ANCA patients [4]. There is no clear evidence reported on large-vessel involvement in ANCA-related vasculitis. A few case reports have described the coincidence of ANCA-related vasculitis and large-vessel vasculitis [5].

Novel coronavirus disease-2019 (COVID-19) has caused a worldwide pandemic in a short time after being first identified in December 2019. A variable spectrum of disease symptoms can be seen in adults, ranging from non-specific symptoms such as fever, cough, myalgia, anorexia, headache to severe complications such as acute respiratory distress syndrome acute kidney failure, and shock. Compared to adults, children are usually asymptomatic or have milder symptoms [6]. During the follow-up period, the post-acute effects of the disease were also noted. Multi-organ involvements such as dyspnea, hypoxemia, arrhythmia, thromboembolic events, neuropsychiatric findings, acute kidney failure, rash, vasculitis, and hyperinflammatory response have been reported among post-COVID findings, both in children and adults [7]. Types of post-COVID vasculitis include thromboembolic events, cutaneous vasculitis, Kawasaki-like vasculitis, myopericarditis, and ANCA-associated vasculitis [7]. Post-COVID ANCA-associated vasculitis were reported in adults and pediatric patients [8, 9]. Herein, we present a case diagnosed as TA with the abdominal aorta, celiac artery, superior mesenteric artery, and renal artery involvement that later on developed ANCA-associated vasculitis with diffuse alveolar hemorrhage (DAH) after COVID-19 infection.

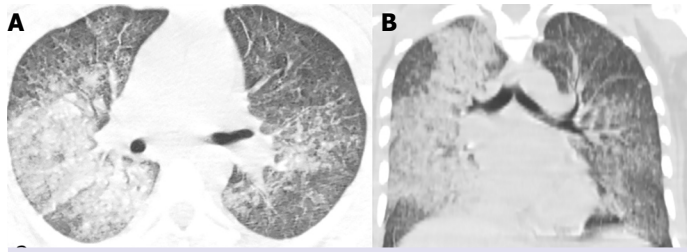

Figure 1. **(A)** In the thorax CT examination performed during her stay in the intensive care unit, there are widespread consolidations and ground-glass densities compatible with alveolar filling. **(B)** In addition, there are crazy paving appearances formed by interstitial lines.

CT: Computed tomography.

CASE REPORT

A 17-year-old female patient was admitted to another hospital with the complaints of cough and bloody vomiting for 2 days. She had lethargy and fine crackles by auscultation of the lungs. She did not have any rash and was normotensive. The family was denying any recent or past exposure to a person with COVID-19 infection. Complete blood count (CBC) showed anemia (hemoglobin [Hg]: 9.4 g/dl) with otherwise normal CBC, normal blood biochemistry, normal acute phase reactants, and normal urinalysis. Two days after hospitalization, she developed tachypnea and dyspnea and was transferred to the pediatric intensive care unit (PICU). The findings on the chest computed tomography (CT) were compatible with acute COVID-19 infection (Fig. 1A, B), but nasopharyngeal swab SARS-CoV2 reverse transcription-polymerase chain reaction (RT PCR) test (Bio-Speedy® SARS-CoV-2N RT-qPCR Kit; sensitivity: 80%, specificity: 98%) was negative. Her Hg level dropped to 4 g/dl and she received red blood cell transfusion.

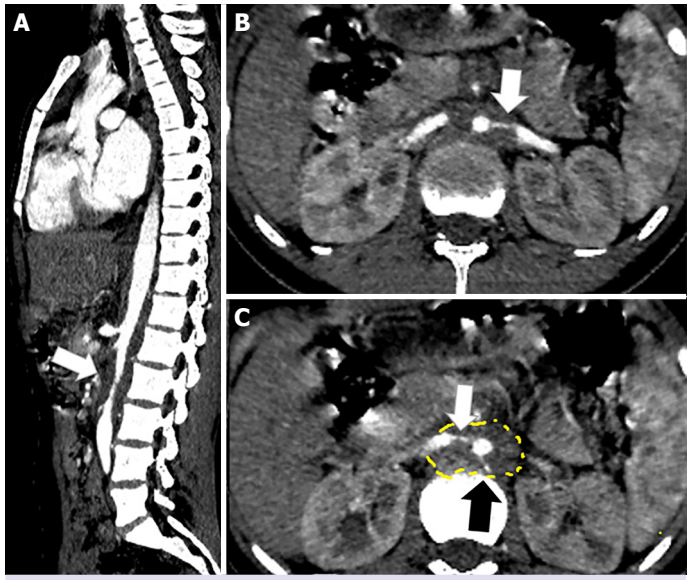

FIGURE 2. **(A)** Thoracoabdominal CT examination. Diffuse wall thickening and narrowing of the lumen are observed in the abdominal aorta on sagittal MR images. The origins of celiac and the superior mesenteric arteries are clearly narrowed. **(B)** On axial CT images, there is marked narrowing of the lumen secondary to all-around wall thickening at the origin of the left renal artery and the right renal artery (arrows). **(C)** There is irregular luminal narrowing secondary to circumferential wall thickening in the abdominal aorta (yellow dotted ring).

CT: Computed tomography.

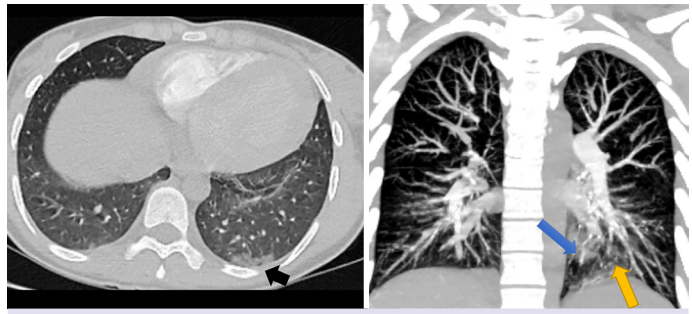

FIGURE 3. In the pulmonary CT angiography performed on the day of hemoptysis, ground-glass densities in the posterobasal region of the left lung lower lobe and filling defects secondary to wall thickening in the distal pulmonary arteries extending to this site are observed.

CT: Computed tomography.

She stayed for 10 days in the PICU and received symptomatic treatment for COVID-19 infection but did not necessitate mechanical ventilation. After stabilization of the general status of the patient, upper gastrointestinal (GI) endoscopy was performed that reported to be normal. Abdominal Doppler ultrasonography revealed wall thickening in the 11–12 cm segment of the abdominal aorta and stenosis in the bilateral renal arteries. The findings of the patient were compatible with TA and acute COVID-19 infection.

She was referred to our clinic for further investigation. Her blood pressure was high (150/95 mmHg), but there were no differences in the four extremities. Lung sounds were clear but there was evident abdominal bruit by auscultation. CBC showed anemia (Hg: 8.3 g/dl) with normal leukocyte count (leukocytes: 6100/mm^3) and normal platelet count (platelets: 345000/mm^3). Acute phase reactants were mildly elevated (C-reactive protein: 15 mg/L and erythrocyte sedimentation rate: 35 mm/h). Urinalysis did not reveal any hematuria or proteinuria. Abdominal CT angiography revealed an increase in abdominal aortic wall thickness, narrowing of the lumen, and stenosis in bilateral renal arteries (Fig. 2A–C). The patient fulfilled the PReS/EULAR/PRINTO classification criteria for TA [10]. Amlodipine was started for hypertension.

In the follow-up, the patient developed hematemesis again and repeat upper GI endoscopy was normal. On the 3rd day of hospitalization, she started to have hemoptysis, tachypnea, dyspnea, and desaturation in the room air and she was transferred to PICU. To evaluate her low oxygen saturation and determine the source of bleeding, chest CT and CT angiography were performed. Diffuse alveolar infiltrates and interlobar septal thickenings were detected on the CT, and there were no COVID-19-related findings in the lungs (Fig. 3). The bronchoscopy showed bronchial mucosal fragility, bleeding foci, and mucosal bleeding. The broncoalveolar lavage (BAL) samples were sterile, and hemosiderin-laden macrophages were seen in the histopathologic examination. Echocardiography revealed that the ejection fraction was 52% and left ventricular contraction was weak. Repeat nasopharyngeal swab SARS-CoV2 RT-PCR test was negative, but serum SARS-CoV2 immunoglobulin (Ig) M and IgG antibody tests (Architect SARS-CoV-2 IgM/IgG Antibody Test Kit; sensitivity: 96.6%, specificity: 99.6%) that were studied on the 3rd week of disease onset were positive. The patient was not vaccinated against COVID-19. Intravenous immune globulin (IVIG) (1 g/kg) and pulse corticosteroid (1 g/day) therapies were started for DAH and post-COVID myocarditis. Hemoptysis persisted despite 3 days of treatment and a single dose of intravenous cy-

clophosphamide was given. Captopril and doxazosin were added to amlodipine to control high blood pressure. The indirect immunofluorescence assay-ANCA test became 3 (+) with MPO-ANCA of 125 RU/ml (normal: <20).

The patient's condition gradually improved and she did not have hemoptysis after immunosuppressive therapy. Control echocardiography was normal. Balloon angioplasty was performed for renal artery stenosis. After angioplasty, her blood pressure was controlled by amlodipine alone. The control MPO-ANCA titers were decreased gradually. The patient is being followed for 6 months under maintenance therapy with low-dose corticosteroids and azathioprine with normotensive blood pressure.

The clinical features, angiographic large, medium, and small vessel abnormalities, positive COVID-19 antibody, and ANCA tests made us the final diagnosis of the patient as having TA with post-COVID ANCA-associated vasculitis.

DISCUSSION

According to the Chapel-Hill classification, primary vasculitides are classified as large, medium, and small size. TA is a chronic granulomatous vasculitis with large vessel involvement. Although the clinical findings vary depending on the stage of the disease and the vascular involvement pattern, the most common are fever, night sweats, weight loss, arthralgia, myalgia, abdominal pain, headache, and hypertension. While pulmonary artery aneurysm, pulmonary infarction, and increase in pulmonary vessel wall thickness are frequently observed, pulmonary capillary involvement is rarely observed in TA [2]. In our case, TA was diagnosed according to PReS/EULAR/PRINTO classification criteria with hypertension accompanying abdominal and renal artery involvement on CT angiography.

Because DAH was detected in thorax CT and BAL findings, she was started to be investigated for small vessel vasculitis. ANCA tests and serum SARS-CoV2 IgM and IgG antibody tests were positive. Since TA rarely involves small vessels and ANCA vasculitis does not involve large vessels, our patient was diagnosed as COVID-associated ANCA vasculitis developed on the basis of TA.

It is thought that COVID-19 may impair immune tolerance and trigger autoimmunity with cross-reaction. Cases reporting the development of post-COVID Guillain-Barré syndrome, systemic lupus erythematosus, or ANCA-associated vasculitis support this theory [11, 12].

When the literature was reviewed, cases of COVID-associated ANCA vasculitis were first described in adults [13]. Only two pediatric cases were reported with MPO-ANCA-positive COVID-associated ANCA vasculitis [9, 14]. The first reported case was a 12-year-old girl who presented with pulmonary and renal involvement, negative for nasopharyngeal swab SARS-CoV2 RT PCR test, and positive for serum SARS-CoV2 IgG antibodies [14]. The patient was treated with methylprednisolone, rituximab, and cyclophosphamide, and clinical improvement was detected. The second case was a 17-year-old male who presented with DAH and acute renal failure infected with COVID-19 2 months ago [14]. He has been successfully treated with plasmapheresis, methylprednisolone, and cyclophosphamide. One case has been reported in pediatric patients with PR3-ANCA-positive COVID-associated ANCA vasculitis. A 17-year-old male patient was found to be positive for PR3 ANCA during active COVID-19 infection and was treated with rituximab and methylprednisolone [15]. In our case, DAH caused by ANCA-associated vasculitis did not show dramatic response to IVIG and pulse corticosteroids but single dose of cyclophosphamide led to the resolution of DAH. She never developed renal involvement throughout the disease course.

In the literature review, we have seen that the coexistence of TA and ANCA-associated vasculitis were reported only in one pediatric patient. An 11-year-old girl presented with DAH and acute renal failure had right and left common carotid artery and right subclavian artery involvement. She also had rapidly progressive glomerulonephritis in kidney biopsy and MPO-ANCA positivity [16]. The patient died due to pulmonary hemorrhage and multiorgan failure despite pulse corticosteroids, cyclophosphamide, plasmapheresis, and dialysis treatments.

To the best of our knowledge, our case is the second case with the coexistence of the TA and ANCA-associated vasculitis.

Informed Consent: Written, informed consent was obtained from the patient's family for the publication of this case report and the accompanying images.

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