Acute ANCA Vasculitis and Asymptomatic COVID-19

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We describe the presentation and diagnosis of a child with newly diagnosed antineutrophil cytoplasmic antibody–associated vasculitis and associated diffuse alveolar hemorrhage who was positive for coronavirus disease 2019 immunoglobulin G antibodies, indicative of a previous asymptomatic infection. Results of multiple polymerase chain reaction tests coinciding with the start of symptoms were negative, indicating that acute infection was not the cause of the patient's symptoms. Coronavirus disease 2019–induced autoimmune diseases have been described in adults, but this case report represents the first case described in a pediatric patient.

The global pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to rapid recognition of coronavirus disease 2019 (COVID-19) and sequelae of the acute infection.[1] The symptoms of COVID-19 are varied, particularly in children, who more frequently have asymptomatic or minimally symptomatic disease or the newly described multisystem inflammatory syndrome in children.[2] The spectrum of disease and potential sequelae from acute infection, particularly in children, is not fully described. We report a case of an adolescent who presented with an antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis causing diffuse alveolar hemorrhage after asymptomatic COVID-19 infection.

CASE

A 12-year-old girl with progressive respiratory failure was transferred to a tertiary children's hospital from a community hospital for further diagnostic evaluation and management. Two weeks before transfer, she had onset of mild, productive cough with blood streaked sputum without any respiratory distress, fevers, rash, bruising, or joint pain. On physical examination by her primary care physician, she had crackles at the left lung base. Community-acquired pneumonia was diagnosed, and amoxicillin was prescribed. Because of high prevalence of COVID-19 in the community (community testing rate of 25%–30% positive results in the week of illness onset), nasopharyngeal swab polymerase chain reaction (PCR) testing for COVID-19 was performed, and the result was negative. Four days later, she had acute onset of bilateral leg and feet pain that led to progressive difficulty with ambulation, prompting admission to a community hospital. On admission, she was afebrile and had a normal respiratory rate, normal oxygen saturations, and a normal heart rate. A physical examination revealed mild swelling of the right knee and left ankle without erythema or warmth and crackles in the left lung base. A chest radiograph revealed left lower lobe consolidation consistent with a previous diagnosis of pneumonia, and the result of repeat nasopharyngeal swab COVID-19 PCR testing was negative. Amoxicillin was discontinued,

abstract

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Drs Powell and Campbell collected clinical history and data and drafted the initial manuscript; Drs Ross and Peña Jiménez collected clinical history and data; Dr Rudzinski performed the pathologic analysis and reviewed clinical history and data; Dr Dickerson performed clinical laboratory testing and reviewed clinical history and data; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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and ceftriaxone, clindamycin, and azithromycin were started. Laboratory findings were notable for the following: white blood cell count of 15.5 $\times$ 10^3/mL, hematocrit value of 30.7%, platelet count of 565 $\times$ 10^3/mL, C-reactive protein level of 10.9 mg/dL, and erythrocyte sedimentation rate of 54 mm/hour. Her knee and ankle pain resolved with acetaminophen, but she had new onset of dyspnea, which resulted in progression over 3 days from room air to requiring low-flow nasal cannula oxygen to requiring 10 L/minute of high-flow nasal cannula supplemental oxygen. A chest computed tomography scan was obtained and revealed dense consolidation in the left lower lobe and patchy infiltrate in the right middle and upper lobes without ground-glass opacities (Fig 1). Because of her worsening respiratory status, she was transferred to a tertiary children's hospital ICU.

On admission to the ICU, she was placed on bilevel positive airway pressure at 22/10 cm H_2O, which resulted in improvement in dyspnea. A physical examination revealed nonblanching, violaceous macules on her right foot, diminished breath sounds in the left lung base and crackles in all lung fields, normal mentation, erythematous oropharynx, normal conjunctiva, and normal neurologic functioning. Because of ongoing community spread of COVID-19, she was placed in airborne isolation precautions. Laboratory findings at the time of transfer were notable for the following: white blood cell count of 13.9 $\times$ 10^3/mL, hematocrit value of 25.7%, platelet count of 530 $\times$ 10^3/mL, C-reactive protein level of 16.4 mg/dL, erythrocyte sedimentation rate of 117 mm/hour, and urinalysis results of 1+ leukocyte esterase, negative nitrites, 3+ microscopic hematuria, and a urine protein/creatinine ratio of 0.25. Repeat nasopharyngeal swabs and induced sputum samples were negative for COVID-19 by PCR testing. Antibody testing was positive for COVID-19 immunoglobulin G (IgG) antibodies. Rheumatology, infectious disease, nephrology, and pulmonology were consulted. Ceftriaxone and clindamycin were discontinued, azithromycin was continued, and vancomycin, cefepime, and fluconazole were initiated. Antibody testing revealed a positive myeloperoxidase antibody (anti-MPO) result as well as a positive ANCA result, with a titer of 1:640 and a perinuclear pattern. Results of Antinuclear antibody, double-stranded DNA antibody, and extractable nuclear antigen panels were negative. C3 and C4 complement levels were normal. Given these results, suspicion for systemic lupus erythematosus was low. Antiphospholipid antibody testing was not performed given low suspicion, but testing could be considered in future cases. Bronchoalveolar lavage was used to diagnose diffuse alveolar hemorrhage consistent with possible vasculitis. Bronchoalveolar lavage fluid was negative for COVID-19 by PCR testing. A renal biopsy specimen revealed a pauci-immune necrotizing and crescentic glomerulonephritis, confirming the diagnosis of anti-MPO ANCA vasculitis with pulmonary and renal involvement. She was initiated on methylprednisolone, rituximab, and cyclophosphamide, which resulted in improvement in her clinical status.

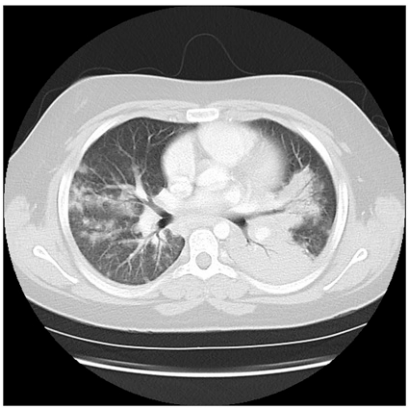

FIGURE 1
Chest computed tomography image revealing left lower lobe consolidation and patchy infiltrate in other lung fields.

DISCUSSION

Here we report the first case of a new-onset anti-MPO vasculitis in an adolescent who tested positive for COVID-19 IgG antibodies. Whether this represents a case of COVID-19–induced vasculitis or a primary autoimmune ANCA vasculitis remains uncertain. She had 5 laboratory-developed PCR tests for COVID-19 performed over 2 weeks from first symptom onset, all of which yielded negative results; as a result, we considered that the antibody result could have been a false-positive or a sign of a cross-reactive antibody. We tested for the COVID-19 IgG antibody was tested using the Abbott Architect SARS-CoV-2 IgG assay, a qualitative test for IgG antibodies against the SARS-CoV-2 nucleoprotein.[3] This patient's index level was elevated at 5.8; false-positives are more common around the cutoff of 1.4, as recommended by the manufacturer, and quantitative antibody titers are not available as part of this assay.[3] Quantitative antibody titers would be useful in future cases describing the immune kinetics after SARS-CoV-2 infection. As part of standard laboratory quality assurance, 5 residual patient samples with positive anti-MPO results were tested by using the same assay, and results of all tests were negative. The positive COVID-19 IgG antibody test is unlikely to be cross-reactivity, as has been reported in another case of positive COVID-19 immunoglobulin M antibody results in the setting of pulmonary vasculitis, given the specificity of this test and absence of cross-reactivity on quality assurance testing.[4] As a result, this case likely represents an asymptomatic case of COVID-19 with subsequent postinfectious development of anti-MPO vasculitis. The precise timing of the

asymptomatic infection in relation to the onset of vasculitis is not known, although IgG antibodies typically arise within 2 to 3 weeks of infection and coincide with viral clearance.[5,6] This patient likely had an asymptomatic infection during the initial surge of cases because she presented 2 to 4 weeks after the first peak of cases in her local area. A viral trigger for the onset of ANCA vasculitis and alveolar hemorrhage has been described with COVID-19 and other viral illnesses.[7–9] COVID-19 with copresentation of ANCA vasculitis causing glomerulonephritis has been described during active viral infection in adult patients.[10] Whether direct infection of renal tissue serves as a trigger for the renal involvement of the ANCA vasculitis remains unknown because detection of virions on the renal biopsy specimen was not performed as part of the clinical care in this case. It will be important to continue to investigate the relationship between COVID-19 infection and new-onset autoimmune diseases, such as thrombocytopenia, neurologic diseases, and Guillain-Barre syndrome.[11–13] Our case offers the novel hypothesis that asymptomatic COVID-19 in children acts as an immune trigger for autoimmune conditions, such as ANCA vasculitis, which should be further tested. To the best of our knowledge, this represents the first case of an asymptomatic infection with the subsequent diagnosis of ANCA vasculitis in a child. This case highlights the need for careful monitoring of long-term sequelae of COVID-19 in children given their frequent asymptomatic or minimally symptomatic infections.

ABBREVIATIONS

ANCA: antineutrophil cytoplasmic antibody
anti-MPO: myeloperoxidase antibody
COVID-19: coronavirus disease 2019
IgG: immunoglobulin G
PCR: polymerase chain reaction
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

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