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Acute ANCA Vasculitis and Asymptomatic COVID-19

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Abbreviations:
MIS-C: multisystem inflammatory syndrome in children
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
WBC: white blood cell count
CRP: c-reactive protein
ESR: erythrocyte sedimentation rate
Anti-MPO: myeloperoxidase antibody
ANCA: Antineutrophil cytoplasmic antibodies
BAL: bronchoalveolar lavage

Article Summary: We describe the case of a child with asymptomatic COVID-19 infection and newly diagnosed ANCA-vasculitis leading to pulmonary hemorrhage.
Contributors’ Statement
Dr. Weston T. Powell and Dr. Julie Campbell collected clinical history and data, drafted the initial manuscript, and reviewed and revised the manuscript.
Dr. Francesca Ross and Dr. Patricia Peña Jimenez collected clinical history and data, and reviewed and revised the manuscript.
Dr. Erin Rudzinski performed pathologic analysis, reviewed clinical history and data, and reviewed and revised the manuscript.
Dr. Jane Dickerson performed clinical laboratory testing, reviewed clinical history and data, and reviewed and revised the manuscript.
All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.
Abstract

We describe the presentation and diagnosis of a child with newly diagnosed ANCA-associated vasculitis and associated diffuse alveolar hemorrhage who was positive for COVID-19 IgG antibodies indicative of a prior asymptomatic infection. Multiple PCR-based tests coinciding with the start of symptoms were negative indicating that acute infection was not the cause of the patient’s symptoms. COVID-19 induced autoimmune diseases have been described in adults, but this represents the first case described in a pediatric patient.

Introduction

The global pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to rapid recognition of the acute disease COVID-19 and sequelae of the acute infection. 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 (MIS-C). 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 ANCA-associated vasculitis causing diffuse alveolar hemorrhage following asymptomatic COVID-19 infection.

Case

A 12-year-old female with progressive respiratory failure was transferred to a tertiary children’s hospital from a community hospital for further diagnostic evaluation and management. Two weeks prior to transfer, she had onset of mild, productive cough with blood streaked sputum without any respiratory distress, fevers, rash, bruising, or joint pain. On physical exam by her primary care physician, she had crackles at the left lung base. Community acquired pneumonia was diagnosed and amoxicillin prescribed. Due to high prevalence of COVID-19 in the community (25-30% positive community testing rate in the week of illness onset),
nasopharyngeal swab PCR testing for COVID-19 was performed and 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 with normal respiratory rate, normal oxygen saturations, and normal heart rate. Physical exam showed mild swelling of the right knee and left ankle without erythema or warmth and crackles in the left lung base. Chest x-ray revealed left lower lobe consolidation consistent with prior diagnosis of pneumonia and repeat nasopharyngeal swab COVID-19 PCR testing was negative. Amoxicillin was discontinued and ceftriaxone, clindamycin, and azithromycin were started. Lab findings were notable for white blood cells (WBC) 15.5x10^3/mL, hematocrit 30.7%, platelets 565 x10^3/mL, c-reactive protein (CRP) 10.9 mg/dL, and erythrocyte sedimentation rate (ESR) 54 mm/hr. Her knee and ankle pain resolved with acetaminophen, but she had new onset of dyspnea with a 3-day progression from room air to requiring low-flow nasal cannula oxygen to 10L/min high-flow nasal cannula with supplemental oxygen. Chest CT was obtained which showed dense consolidation in the left lower lobe and patchy infiltrate in the right middle and upper lobes without ground-glass opacities. (Figure 1). Due to her worsening respiratory status, she was transferred to a tertiary children’s hospital intensive care unit.

On admission to the intensive care unit, she was placed on Bi-Level positive airway pressure at 22/10 cm H2O with improvement in dyspnea. Physical exam revealed non-blanching, 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, normal mentation and normal neurologic exam. Due to ongoing community spread of COVID-19, she was placed in airborne isolation precautions. Lab findings at time of transfer were notable for WBC 13.9 x10^3/mL, hematocrit 25.7%, platelet 530 x10^3/mL, CRP 16.4 mg/dL, ESR 117 mm/hr, and
urinalysis with 1+ leukocyte esterase, negative nitrites, 3+ microscopic hematuria, and urine protein:creatinine ratio 0.25. Repeat nasopharyngeal swabs and induced sputum samples for COVID-19 were negative by PCR testing. Antibody testing was positive for COVID-19 IgG. 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 positive myeloperoxidase antibody (anti-MPO) and positive antineutrophil cytoplasmic antibodies (ANCA) titer 1:640 with a P-ANCA pattern. Anti-nuclear antibody, double stranded DNA antibody, and extractable nuclear antigen panel were negative. C3 and C4 complement levels were normal. Given these results, suspicion for systemic lupus erythematosus was low. Anti-phospholipid antibody testing was not performed given low suspicion, but testing could be considered in future cases. Bronchoalveolar lavage (BAL) diagnosed diffuse alveolar hemorrhage consistent with possible vasculitis. BAL fluid was negative for COVID-19 by PCR testing. Renal biopsy demonstrated 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 with improvement in clinical status.

**Discussion**

Here we report the first case of a new onset anti-MPO vasculitis in an adolescent with positive COVID-19 IgG antibody. Whether this represents a case of COVID-19 induced vasculitis or a primary auto-immune 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 were negative; as a result, we considered that the antibody could be a false positive or a cross-reactive antibody. COVID IgG antibody was tested using the Abbott Architect SARS-CoV-2 IgG Assay,
a qualitative test for IgG against the SARS-CoV-2 nucleoprotein. This patient’s index was elevated at 5.8; false positives are more common around the cut-off of 1.4 recommended by the manufacturer, and quantitative antibody titers are not available as part of this assay. Quantitative antibody titers would be useful in future cases describing the immune kinetics following SARS-CoV-2 infection. As part of standard lab quality assurance, five residual patient samples with positive anti-MPO were tested using the same assay, and all were negative. This is unlikely to be cross-reactivity as has been reported in another case of positive COVID-19 IgM antibody in the setting of pulmonary vasculitis, given the specificity of this test and absence of cross-reactivity on quality assurance testing. As a result, this likely represents an asymptomatic case of COVID-19 with subsequent post-infectious 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 2-3 weeks of infection and coincide with viral clearance. This patient likely had an asymptomatic infection during the initial surge of cases as she presented 2-4 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. COVID-19 with co-presentation of ANCA vasculitis causing glomerulonephritis has been described during active viral infection in adult patients. Whether direct infection of renal tissue serves as a trigger for the renal involvement of the ANCA vasculitis remains unknown as detection of virions on the renal biopsy sample 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. 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 an 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.

References


Figure 1. Chest CT image demonstrating left lower lobe consolidation and patchy infiltrate in other lung fields.
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