A case of ANCA-associated vasculitis in a 16-year-old female following SARS-COV-2 infection and a systematic review of the literature

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Case Report

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Abstract

Background: Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a rare form of vasculitis in children. SARS-CoV-2, the virus that causes COVID-19 infection, seems to trigger autoimmunity and new-onset autoimmune disease in pediatric and adult patients. We present a case of new-onset AAV following COVID-19 infection in an adolescent patient, and we review the literature of AAV following COVID-19 infection.

Case presentation: An adolescent female with a history of asthma was diagnosed with mild COVID-19 infection and subsequently developed persistent cough, wheezing, hearing loss, arthralgias, and rash. Her imaging and laboratory workup showed pulmonary nodules and cavitary lesions, elevated inflammatory markers, negative infectious testing, and positive ANCA. She was treated with corticosteroids, rituximab, and mycophenolate. At six-month follow-up, she had improvement in her symptoms, pulmonary function tests, imaging findings, and laboratory markers.

Conclusions: We report the second case of new-onset anti-PR3, C-ANCA vasculitis and the fourth case of pediatric-onset AAV following COVID-19 infection. A systematic review of the literature found 6 cases of new-onset AAV in adults after COVID-19 infection. Pediatric and adult patients who develop AAV post COVID-19 infection have few, if any, comorbidities, and show marked radiographic and symptomatic improvement after treatment. There is increasing evidence for COVID-19-induced autoimmunity in children and our case highlights the importance of considering AAV in a child following a recent COVID-19 infection because timely treatment may improve clinical outcomes.

Background

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a rare form of vasculitis in children with an estimated annual incidence of < 1 per one million children.[1–4] Granulomatosis with polyangiitis (GPA), one of the ANCA-associated vasculitides, is a systemic, necrotizing vasculitis with granulomatous inflammation that typically affects the upper and lower respiratory tract and kidneys.[5] It often presents with nonspecific symptoms including fever, malaise, weight loss, anorexia, myalgias and arthralgias. Although the mechanism of pathogenesis is not fully understood, AAV is thought to be immune-mediated with a chronic and relapsing course.[6]

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused significant morbidity and mortality since it was first reported in late 2019.[7] SARS-CoV-2, similar to other viruses, seems to trigger autoimmunity in both the pediatric and adult populations.[8–11] Acute COVID-19 infection causes less severe symptoms in the pediatric population;[12,13] however, a small percentage of children subsequently develop immune-mediated disease after COVID-19 infection.[8,9,14] We present a case of new onset AAV, most consistent with GPA, following COVID-19 infection in a 16-year-old female, and we review the literature of AAV following COVID-19 infection to highlight another potential SARS-COV-2 triggered immune-mediated disease in the pediatric population.

Case Presentation

A 16-year-old female with a past medical history significant for asthma was referred to the pediatric pulmonology clinic by her pediatrician for persistent cough and wheezing following COVID-19 infection.

Approximately 1 week after recovering from a mild COVID-19 infection diagnosed via PCR testing after a positive rapid antigen test, she developed wheezing and a prominent, non-productive cough that worsened at night and persisted throughout the day. She was initially treated by her pediatrician with albuterol which helped her wheezing but not her cough. A chest x-ray at that time was normal. Over the next month, her symptoms progressed to include sinus pain, serosanguinous ear drainage, and a sensation of fullness in her ears. Her pediatrician treated her with courses of azithromycin, cefdinir, and doxycycline. The antibiotics did not resolve her symptoms and she was trialed on a 5-day course of prednisone (60 mg daily). She saw otolaryngology who diagnosed her with chronic bilateral serous otitis media and recommended tympanostomy tube placement. She underwent tympanostomy tube placement with some relief in her symptoms but reported ongoing bilateral hearing loss which did not improve after the procedure.

When she presented to pediatric pulmonology 6 weeks after the onset of her symptoms, she was still wheezing and had a daily paroxysmal cough with occasional post-tussive emesis. She also reported chest tightness and difficulty breathing. She had a chest x-ray which showed patchy airspace disease of the upper lungs, concerning for a multifocal infectious or inflammatory process. Her symptoms suggested an exacerbation of asthma for which she was prescribed another 5-day course of prednisone (40 mg twice daily), albuterol, and she was started on inhaled corticosteroids in combination with a long-acting beta agonist. Her symptoms improved initially but returned as soon as she stopped taking systemic steroids. Over the next 5 weeks, the patient's cough became productive of green sputum with worsening wheezing that was no longer responsive to bronchodilators. She was treated with a 28-day course of cefdinir for protracted bacterial bronchitis. When she returned for follow up three months later, she continued to complain of cough and wheezing with new onset myalgias. She underwent pulmonary function testing which showed moderate post-bronchodilation small airway obstruction.

Chest x-ray revealed perihilar and bilateral upper lobe consolidations that represented a significant progression from her previous x-ray 3 months prior. High resolution chest CT demonstrated extensive multifocal pulmonary nodules and regions of consolidation with multiple areas of cavitation and central bronchiectasis with diffuse bronchial wall thickening as well as reactive mediastinal and hilar adenopathy (Figure A). CT findings were concerning for allergic bronchopulmonary aspergillosis or chronic pulmonary aspergillosis. However, the patient underwent aspergillus antibody studies which were negative. (1–3) Beta-D-Glucan (Fungitell) assay was negative. No IFN-gamma response to M tuberculosis antigens was detected (Quantiferon assay). Induced sputum culture was negative for bacteria, fungal organisms, and acid-fast bacilli. Other labs were notable for elevated inflammatory markers with a c-reactive protein of 12 and an erythrocyte sedimentation rate of 30. Her ANCA screen was positive: her C-ANCA was positive at 1:40. P-ANCA was negative. Proteinase 3 antibody (anti-PR3) was positive at 1.4.

Beta 2 Glycoprotein 1 IgM and IgG were negative; anticardiolipin antibodies were negative; Complement C3 was 165 and Complement C4 was 23. Serum creatinine and urinalysis were normal. She was referred to pediatric rheumatology for concern of systemic vasculitis.

When she presented to pediatric rheumatology, her review of systems was noteworthy for a 45-pound weight loss; intermittent conjunctivitis; sinus congestion, nasal congestion, bilateral hearing loss, ear drainage, sinus headaches, nosebleeds; cough, wheezing and shortness of breath; progressively worsening bilateral arthralgias in her knees, feet and elbows that improved with activity; intermittent rashes, and sun sensitivity.

She underwent lung tissue biopsy which showed non-specific findings with focal areas of parenchymal atelectasis as well as scattered intra-alveolar macrophages. There was no evidence of acute or granulomatous inflammation or vasculitis identified in the biopsied specimen. There were no yeast or fungal elements seen.

Our patient's clinical presentation and positive serology is most consistent with GPA. To induce remission, she was started on rituximab infusions which she tolerated well. She completed a steroid taper and was started on mycophenolate as maintenance therapy. At her most recent follow up, she reported a marked improvement in her symptoms although she continues to have bilateral hearing loss necessitating hearing aids. Repeat CT imaging showed an overall improvement in the extent of previously seen multifocal consolidation, nodularity, and cavitation in her lungs (Figure B). She demonstrated significant improvement in her pulmonary function tests.

Search Strategy And Literature Review

The authors conducted a systematic review of the literature from December 1, 2019 to January 1, 2022, in PubMed, combining the MeSH search terms (COVID-19) AND (ANCA-associated vasculitis), filtered by age (birth-18) and date (Jan. 1, 2019-Jan. 1, 2022); ((Adolescent) AND (COVID-19) AND (ANCA-associated vasculitis)); ((Pediatric) AND (COVID-19) AND (ANCA-associated vasculitis)). Clinical studies, case reports, and case series reporting ANCA-associated vasculitis after COVID-19 infection in the pediatric population were included. Two authors (MCB, AY) independently screened titles, abstracts, and full texts of all relevant articles. The search results were reviewed by the two authors and the included articles were agreed upon. From each article, the authors collected data on publication year, age, gender, comorbidities, chronicity with COVID-19 infection, laboratory tests, serological profile, lung pathology, kidney pathology, AAV therapy, and outcomes.

Discussion And Conclusion

Here we report the second case of new-onset anti-PR3, C-ANCA vasculitis and the fourth case of AAV following COVID-19 infection in the pediatric population. The gold standard for diagnosing childhood vasculitis is with either histopathology from tissue biopsy or by characteristic lesions detected by

imaging studies. Multiple studies in adults have found that more than half of biopsies reveal only non-specific inflammation with necrosis,[15–17] which is what the lung biopsy of our patient showed. Different classification criteria have been proposed to diagnose GPA in children.[5,18–20] The mostly commonly used classification system in pediatrics is the European League Against Rheumatism/Pediatric Rheumatology International Trials Organization/Pediatric Rheumatology European Society (EULAR/PRINTO/PRES) classification scheme; it requires three of the following six features to diagnose GPA: abnormal urinalysis with hematuria or proteinuria; nasal sinus inflammation; granulomatous inflammation on biopsy; subglottic, tracheal or endobronchial stenosis; abnormal chest x-ray or CT; PR3-ANCA or C-ANCA positivity.[5,18,21] Most patients (> 80%) have a positive ANCA, and GPA is primarily associated with PR3-ANCA.[22,23] Approximately 90% of patients with GPA have ENT manifestations such as rhinosinusitis, otitis media, earache, conductive and/or sensorineural hearing loss, persistent rhinorrhea, purulent or bloody nasal discharge.[24–26] Our patient meets criteria for AAV and her clinical presentation—nasal sinus inflammation, upper airway and middle ear involvement, abnormal CT showing cavitary lesions, and PR3 and C-ANCA positivity—is most consistent with GPA.[18]

With the present report, we identified three cases of pediatric-onset ANCA-associated vasculitis (PAAV) and the table includes an update of the published cases (Table 1). A review of the literature found three cases of PAAV following COVID-19 infection. A total of four cases were included in this review.[27–29] Of the four patients (including ours), two (50%) were male; the mean age was 15.5 +/- 2.1 years.[27–29] Two of the patients had no prior comorbidities while two had pre-existing asthma.[29] Immunological tests showed positive C-ANCA in two cases[27] and P-ANCA in two.[28,29] Two patients had anti-PR3 antibodies,[27] and 2 patients had anti-MPO antibodies.[28,29] Pulmonary imaging studies showed multifocal cavitary pulmonary nodules in 2 patients;[27] diffuse alveolar hemorrhage in two patients;[28,29] dense patchy infiltrates in 2 patients.[28,29] Two patients had normal kidney function at the time of presentation[27] while two patients had necrotizing glomerulonephritis on renal biopsy.[28,29] All four patients were treated with glucocorticoids. Three patients received rituximab therapy[27,28] and one patient received plasmapheresis;[29] for maintenance therapy, two were treated with cyclophosphamide,[28,29] one was treated with mycophenolate, and one did not continue therapy.[27] All four patients had symptomatic and radiographic improvement at follow up.[27–29]

There have been six reported cases of adults developing AAV following COVID-19 infection.[30] Similar to our findings, half of the adult patients had C-ANCA vasculitis with anti-PR3 antibodies. The most common lung findings were bilateral cavitary lesions, pulmonary infiltrates, and alveolar hemorrhage which were similar to the findings in children. Kidney involvement was more severe in the adults who developed AAV.[30–33] All adult patients (6) had either crescentic or necrotizing glomerulonephritis on renal biopsy, active urinary sediment, and high creatinine levels. Two patients had kidney failure that required hemodialysis.[30–33] The pediatric patients who developed renal involvement had necrotizing glomerulonephritis on renal biopsy but neither required hemodialysis.[28,29] Two had normal creatinine levels and renal function at presentation.[27] Studies from the NIH report that glomerulonephritis is present

in only 18% of patients at presentation.[24] However, 77 to 85% of patients subsequently develop glomerulonephritis, usually within the first two years of disease onset.[24,34]

The treatment strategy was similar in adults and children with all 10 patients receiving high dose systemic corticosteroids.[27–33] Glucocorticoids have been the standard of care for chronic vasculitis in children.[35,36] Half of the patients (5) received rituximab[27,28,31] and half (5) received cyclophosphamide.[28–30, 32] Cyclophosphamide is often added for patients with more severe disease.[37] Other immunosuppressive medications, such as methotrexate and azathioprine, as well as biologic agents (e.g., TNF-inhibitors, rituximab, and tocilizumab) are increasingly being used to treat chronic vasculitis in the pediatric population.[36,38]

The clinical outcomes following treatment were generally favorable in both adult and pediatric patients: all patients had symptomatic and radiographic improvement; the patients with renal involvement had improvement or resolution of their hematuria, proteinuria and creatinine levels at follow-up; none of the patients required long-term dialysis; Two patients (one pediatric patient and one adult patient) had bilateral hearing loss as part of their initial presentation.[30] Unfortunately, both continued to have profound hearing loss with the need for hearing aids or cochlear implants.[30]

Our case presentation and review of the pediatric and adult literature show that AAV may be another autoimmune-mediated sequela of COVID-19. We report the tenth case of AAV following COVID-19 infection. In general, patients who develop AAV post COVID-19 have few, if any, comorbidities, and show marked radiographic and symptomatic improvement after treatment.

Autoimmunity may be generated by a combination of genetic, hormonal, and environmental factors in susceptible people.[39,40] One such environmental trigger is viral illness. Studies have suggested a causal relationship between viral infections and the onset of autoimmune disease with molecular mimicry, hyperstimulation and dysregulation of the immune system being proposed mechanisms.[10] Epstein-Barr virus, cytomegalovirus, and human immunodeficiency virus are examples of viruses that have an established association to multiple autoimmune diseases.[41–43] There is increasing evidence that SARS-CoV-2 is another virus that can lead to dysregulation of the immune system and the development of autoimmune disease in children and adults.[11] A recent study found that children with a history of COVID-19 infection were at an increased risk of developing type 1 diabetes mellitus than those without a history of COVID-19.[9] Antecedent viral infections have been implicated in the development of PAAV including GPA.[44] Our report and review of the literature suggest that COVID-19 may be another viral trigger for the development of AAV in children and adults. More research is needed to better understand how SARS-CoV-2 may act as a precipitating trigger of autoimmunity and autoimmune disease in children. Our case highlights the importance of considering AAV in a pediatric patient presenting with pulmonary and renal disease following a recent COVID-19 infection because timely treatment may improve clinical outcomes.[44]

Abbreviations

ANCA
Antineutrophil cytoplasmic antibody
AAV
ANCA-associated vasculitis
COVID-19
Coronavirus disease 2019
GPA
Granulomatosis with polyangiitis
PAAV
Pediatric-onset ANCA-associated vasculitis
SARS-CoV-2
Severe acute respiratory syndrome coronavirus 2

Declarations

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Authors' Contributions

A.Y. and L.T.S carried out the patient's medical treatment. M.C.B and A.Y carried out the review of literature. M.C.B drafted the manuscript. All authors proof-read and approved the final version of the manuscript.

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Availability of Data and Materials

All data regarding this study has been reported in the manuscript. Please contact the corresponding author if you are interested in any further information.

Declarations

Ethics approval and consent to participate

The present study was exempt from review by the Institutional Review Board of The Warren Alpert Medical School of Brown University and Lifespan Health System.

Consent for publication

Written informed consent was obtained from the patient's parents regarding the publication of this case report. The purpose of this research was completely explained to the parents and the patient, and they were assured that their information would be kept confidential by the researchers.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 is available in the Supplementary Files section.

Figures

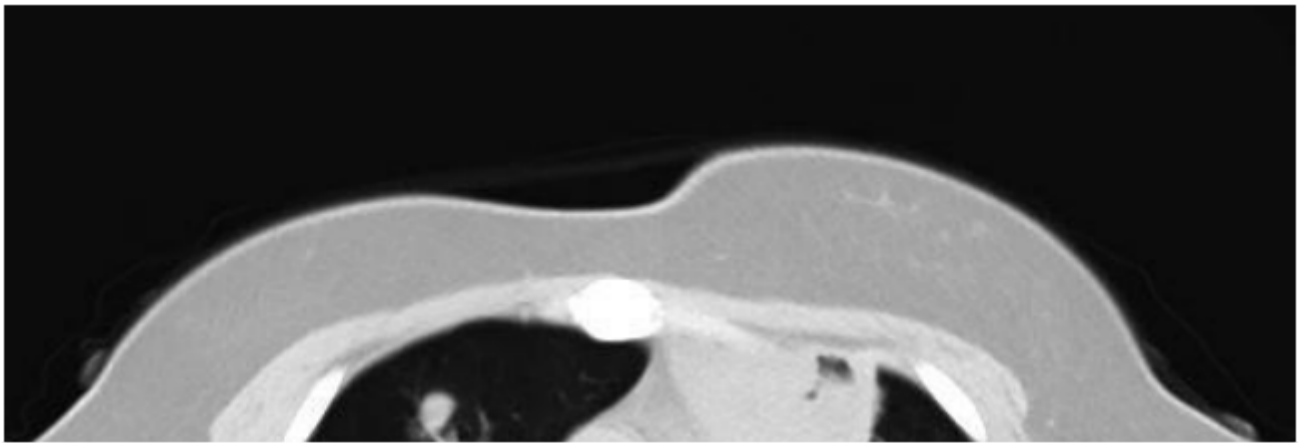

Figure 1

High resolution CT chest taken four months after the onset of symptoms shows extensive multifocal pulmonary nodules and regions of consolidation with areas of cavitation and central bronchiectasis.

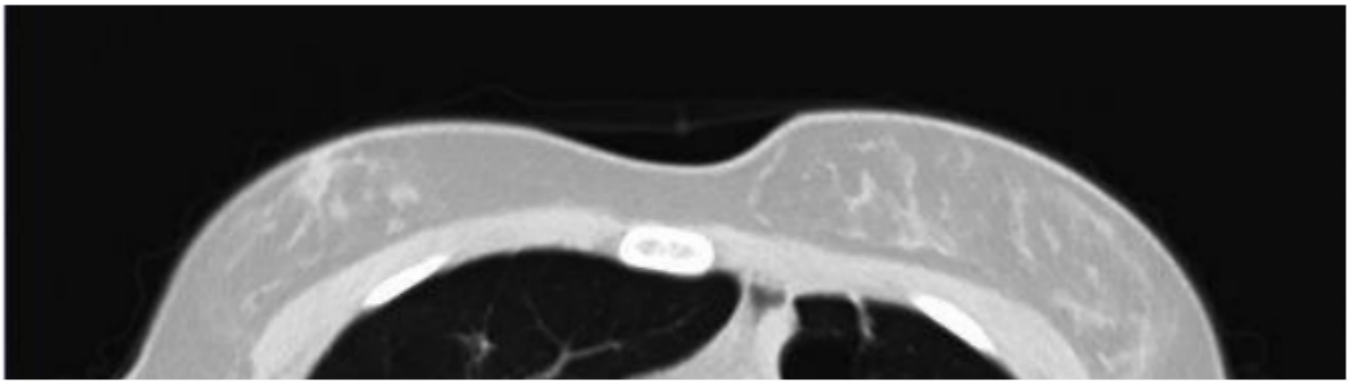

Figure 2

Repeat high resolution CT chest taken 7 months after initial imaging (Figure A) shows an overall improvement in the extent of previously seen multifocal consolidation, nodularity, and cavitation in the lungs, with scattered regions of scarring and several persistent but much smaller nodules. Patient had successfully completed systemic corticosteroid and rituximab treatment at the time of imaging.

Supplementary Files

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