Pathology findings in pediatric patients with COVID-19 and kidney dysfunction

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Abstract

Background. Acute kidney injury (AKI) is seen in one-fifth of pediatric patients with COVID-19 requiring hospital admission, and is associated with increased morbidity, mortality, and residual kidney impairment. The majority of kidney pathology data in patients with COVID-19 is derived from adult case series and there is an overall lack of histologic data for most pediatric patients with COVID-19.

Methods. We assembled a multi-institutional cohort of five unvaccinated pediatric patients with COVID-19 and associated kidney dysfunction with available histology.

Results. Three complex patients with current or prior SARS-CoV-2 infection had multifactorial thrombotic microangiopathy with clinical features of hemolytic uremic syndrome (in two) or disseminated intravascular coagulation (in one); one died and another developed chronic kidney disease stage 5. Two with recently preceding SARS-CoV-2 infection presented with nephrotic syndrome; one had IgA vasculitis and one had minimal change disease. Within a short follow-up time, none has returned to baseline kidney function.

Conclusion. Although uncommon, COVID-19-associated kidney injury can have significant morbidity in the unvaccinated pediatric and adolescent population.

Keywords. Kidney biopsy · Renal pathology · COVID-19 · SARS-CoV-2 · Kidney dysfunction · AKI · Acute kidney injury · Proteinuric · Nephrotic syndrome · TMA · Thrombotic microangiopathy · HUS · Hemolytic uremic syndrome · Glomerulonephritis · Henoch-Schönlein purpura · HSP · IgA vasculitis

Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and associated COVID-19 disease in the pediatric population have generally mild symptomatology and low mortality [1]. Acute kidney injury (AKI) is seen in one-fifth of pediatric patients requiring hospital admission, and is associated with increased morbidity, mortality, and residual kidney impairment [2–4]. The majority of kidney pathology data in patients with COVID-19 is derived from adult case series; investigators have described pathologic findings in a few recent case reports [5–9], but there is an overall lack of histologic data for most pediatric patients. We sought to better understand the histopathology and clinical findings in pediatric patients with COVID-19-associated kidney dysfunction.

Methods

This study was approved by the Institutional Review Boards (IRB) and adheres to the Declaration of Helsinki. Native kidney pathology databases were searched from 2020 to 2021 for pediatric patients ≤ 18 years of age with
COVID-19 and available kidney pathology at Oregon Health and Science University and Doernbecher Children’s Hospital, Stanford University and Lucile Packard Children’s Hospital, and Children’s Hospital of Philadelphia. Biopsies had standard pathologic workup, including light microscopic evaluation with Jones methenamine silver, periodic acid Schiff (PAS), hematoxylin and eosin (H&E), and trichrome stains. For immunofluorescence (IF) microscopy, frozen tissue was stained with antibodies against IgG, IgA, IgM, C3, C1q, fibrin/fibrinogen, and kappa and lambda light chains. Electron microscopic (EM) evaluation followed standard protocols. Clinical history was obtained through discussion with nephrologists and review of the medical record. Coronavirus-like particles were not seen on EM, and SARS-CoV-2 tissue testing was not performed on any of the kidneys as we and others have not identified SARS-CoV-2 in kidney biopsy tissue in previous studies [10–12].

Results

Five pediatric patients with COVID-19 and associated kidney dysfunction had kidney histology available (4 kidney biopsies, 1 autopsy), performed between December 2020 and September 2021. None had been vaccinated against COVID-19. During this time period, the cumulative incidence of COVID-19-associated hospitalizations in children was approximately 49.7 per 100,000 (March 2020–August 2021) [13]; weekly hospitalization rates varied 5–tenfold by time period, age group, and vaccination status. With the emergence of the Delta variant, higher rates of hospitalization, need for invasive mechanical ventilation, and death were observed during the summer of 2021 [13]. During this time period, there were no approved COVID-19 vaccines in the USA for children under the age of 12. Children aged ≥12 years were eligible to receive Pfizer-BioNTech COVID-19 vaccine prior to the emergence of the Delta variant in May 2021. Although viral genotyping was not performed, cases 2 and 5 occurred during winter/spring of 2020–21, during which Alpha and Epsilon were the dominant SARS-CoV-2 variants in the USA. Cases 1, 3, and 4 occurred during summer/fall 2021, during which time Delta was the dominant SARS-CoV-2 variant.

The cohort included 3 males and 2 females aged 5 to 18 years; 3 presented with AKI and had systemic features of thrombotic microangiopathy (TMA), hemolytic uremic syndrome (HUS), or disseminated intravascular coagulation (DIC). Two presented with nephrotic syndrome, which was accompanied by severe abdominal pain and hematochezia in one. Clinical and pathologic findings are summarized by case below, and in Table 1.

Table 1

| Case | Age, sex | Clinical presentation | COVID-19 symptoms, timing | Biopsy findings | Treatment, outcome |
|------|----------|-----------------------|--------------------------|----------------|--------------------|
| 1    | 12 yo F  | New onset DKA, AKI and respiratory symptoms | Respiratory symptoms, + SARS-CoV-2 PCR at presentation, with ARDS | Extensive cortical necrosis and associated thrombosis | Autopsy with acute TMA and pulmonary ARDS Patient died of disease within a week |
| 2    | 6 yo M   | HUS with bloody diarrhea and STEC | HUS with bloody diarrhea and STEC | Acute TMA, acute tubular necrosis | Extensive cortical necrosis and associated thrombosis |
| 3    | 9 yo M   | HUS with severe AKI, non-bloody diarrhea, negative Shiga toxin studies | Acute TMA with ARDS | Acute TMA, acute tubular necrosis | Extensive cortical necrosis and associated thrombosis |
| 4    | 5 yo M   | Nephrotic syndrome, severe abdominal pain, hematochezia to rash | Nephrotic syndrome, severe abdominal pain, hematochezia to rash | HSP nephritis with subendothelial immune complex deposition and endocapillary proliferation | Steroids, mycophenolate. Subsequent central venous catheteritis and central venous catheter-related sepsis |
| 5    | 18 yo F  | Nephrotic syndrome, respiratory symptoms | Respiratory symptoms, + SARS-CoV-2 PCR at biopsy | Minimal change disease with treatment effect and subnephrotic proteinuria | Treated with steroids. One relapse, continued nephrotic syndrome at 3.5 months |

AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; HUS, hemolytic uremic syndrome; DKA, diabetic ketoacidosis; HSP, Henoch-Schönlein purpura; IVIG, intravenous immune globulin; MIS-C, multisystem inflammatory syndrome in children; STEC, Shiga toxin producing E. coli; TMA, thrombotic microangiopathy; CKD, chronic kidney disease.
Case 1

A 12-year-old White female with a history of autism, obstructive sleep apnea, and recurrent urinary tract infections presented with new onset diabetic ketoacidosis (DKA) and altered mental status after a few days of fever, malaise, cough, and chest pain. She was found to have a positive SARS-CoV-2 PCR, and chest X-ray showed pneumonia. After initial response to DKA therapy, she developed worsening respiratory distress and was intubated, subsequently suffering 3 cardiac arrests and was placed on ECMO. Over the following few days, she experienced persistent COVID-19 acute respiratory distress syndrome (ARDS) with refractory hypoxia, myocardial dysfunction, vasopressor refractory shock, altered mental status, AKI, DIC, and marked electrolyte abnormalities (severe hypophosphatemia and hypokalemia). Due to concern for neurologic sequela from multiple cardiac arrests, the family elected comfort care and the patient died a few days after initial presentation.

Postmortem evaluation revealed TMA involving glomerular capillaries (Fig. 1A) and histologic features of ARDS with pulmonary alveolar hyaline membranes, pulmonary parenchymal necrosis, and arterial thromboses. *Staphylococcus aureus* grew from post-mortem lung cultures.

Case 2

A 6-year-old Hispanic male with no significant past medical history presented with a 3-day history of abdominal pain, emesis, and hematochezia. He had initially normal kidney function (serum creatinine (Cr) 0.5 mg/dL) (reference range 0.3–0.7 mg/dL) and platelet count, but quickly developed anemia (hemoglobin 11 g/dL) (reference range 11.5–15.5 g/dL), thrombocytopenia (platelets 35,000/μL) (reference range 150,000–440,000/μL), and AKI (Cr 3.4 mg/dL). Stool was positive for Shiga toxin producing *Escherichia coli* (STEC), leading to a diagnosis of Shiga toxin diarrhea + HUS. He was admitted and developed respiratory distress, SARS-CoV-2 infection, and later multi-system inflammatory syndrome in children (MIS-C) with cardiac involvement manifested as dilatation of left main, left anterior descending, and right coronary arteries, and biatrial dilatation with pericardial effusion.

During a prolonged hospitalization and pediatric intensive care unit (PICU) stay, the patient was treated with pulse solumedrol (30 mg/kg × 3 days), intravenous immune globulin (IVIg), plasmapheresis (5 rounds), and dialysis. Kidney biopsy performed due to lack of kidney recovery demonstrated extensive cortical necrosis and thrombosis involving the entire biopsy core with all sampled vasculature including glomeruli, arterioles, and interlobular arteries (Fig. 1B). Given severity of his clinical course, genetic testing was performed and was negative for abnormalities of the alternative complement pathway (in *ADAMTS13*, *C2*, *C3*, *C3AR1*, *CD46* (MCP), *CFB*, *CFD*, *CFH*, *CFHR1*, *CFHR2*, *CFHR3*, *CFHR4*, *CFHR5*, *CFI*, *DGKE*, *MASP2*, *MMACHC*, *THBD*, *PLG*, *WT1*, and *C5* p.Arg885, Machaon Diagnostics). The extent of renal cortical necrosis and thrombosis was considered likely due to a combination of Shiga toxin diarrhea + HUS and COVID-19 with associated MIS-C. At 7 months, echocardiogram demonstrated normalization of cardiac abnormalities, but he remained dialysis-dependent and was undergoing evaluation for kidney transplant.

Case 3

A 9-year-old White male, previously healthy, who had not received any typical childhood vaccines presented with 2 weeks of fever, nausea, and non-bloody diarrhea. On
presentation, he was hypertensive (136/86) and laboratory studies were concerning for HUS, with hemoglobin of 9.3 g/dL, platelets 148,000/uL, LDH 1835 U/L (reference range ≤ 350 U/L), and schistocytes on blood smear. He had AKI with Cr of 20.9 mg/dL, BUN of 256 mg/dL (reference range 8–25 mg/dL), hematuria, and nephrotic range proteinuria with a urinal protein to creatinine ratio (UPCR) of 8.07 mg/mg (reference range < 0.10 mg/mg). PCR for SARS-CoV-2 was negative but COVID-19 antibodies were detected at admission, with unknown time of infection. Infectious workup was otherwise negative including stool studies which were negative for Shiga toxins 1 and 2, Shigella, and enteropathogenic viruses and bacteria, and negative hepatitis B and anti-DNase B.

A kidney biopsy was performed due to concern for TMA, and demonstrated acute TMA and acute tubular necrosis (Fig. 1C). Results of a TMA functional panel including CH50 level, alternative pathway functional assay, C3b deposition, factor H autoantibody, C3 level, C4 level, factor B, Bb level, soluble C5b-9 (sMAC), factor H level, and factor I levels were all within normal limits (University of Iowa). Genetic testing for abnormalities associated with atypical HUS was negative for clinically significant mutations (Machaon Diagnostics). Thus, despite extensive workup, a definitive etiology for the episode of HUS was not identified, with prior SARS-CoV-2 infection representing a potential trigger. He was treated with inpatient hemodialysis, supportive care, and anti-hypertensives (amlodipine, isradipine as needed) without immunosuppressants. At 6 weeks follow-up, kidney function, proteinuria, and TMA labs had improved but he had persistent renal insufficiency (Cr 0.9 mg/dL) with subnephrotic proteinuria (UPCR 1.02 mg/mg). At 3 months follow-up, Cr improved to 0.6 mg/dL (eGFR 100 mL/min 1.73m²), considered chronic kidney disease (CKD) stage I.

**Case 4**

A 5-year-old, White male, previously healthy, presented with cough and was found to have a positive SARS-CoV-2 PCR. Approximately 2 weeks later, he experienced progressive, severe abdominal pain with palpable purpura and petechial rash, hematochezia, microscopic hematuria, and nephrotic syndrome with hypoalbuminemia (2.1 g/dL, reference range 3.5–5.5 g/dL), proteinuria (UPCR 9.88 mg/mg), hypertension, and edema with weight gain (10 lbs.) with a normal creatinine (0.29 mg/dL). Due to concern for Henoch-Schönlein purpura (HSP) nephritis/IgA vasculitis following COVID-19, a kidney biopsy was performed and revealed HSP nephritis/IgA vasculitis with diffuse endocapillary hypercellularity, focal crescents (5%), moderate podocyte foot process effacement, and endothelial tubuloreticular inclusions (Fig. 2). He was treated with IV pulse steroids (methylprednisolone 30 mg/kg/day) followed by oral steroids (prednisolone 2 mg/kg/day) with weekly solumedrol infusions (30 mg/kg); mycophenolate mofetil followed by enalapril was subsequently added due to ongoing proteinuria. Nephrotic syndrome was managed with 25% albumin and furosemide. A few days after discharge, he was readmitted with severe headache and found to have a cerebral venous sinus thrombosis, which was treated with enoxaparin. He continued to have nephrotic range proteinuria (UPCR 3.79 mg/mg) at 6 weeks, and had multiple readmissions for severe headaches. At 3.5 months of follow-up, headaches had improved, Cr remained within normal limits, and proteinuria had decreased to 1.4 mg/mg.

**Case 5**

An 18-year-old Hispanic female with no significant past medical history presented with swelling and was found to have nephrotic syndrome with hypoalbuminemia (2.2 g/
dL), hyperlipidemia (total cholesterol 405 mg/dL, reference range < 200 mg/dL), and 7.79 g of proteinuria on calculated 24-h urine. She was positive for SARS-CoV-2 by PCR and reported respiratory symptoms 1 month prior which had resolved by the time of presentation for edema. Other laboratory tests including antinuclear antibodies (ANA) and complement levels were negative/normal. She was treated with prednisone (60 mg/day). A subsequent kidney biopsy performed to determine histologic diagnosis for apparently steroid sensitive nephrotic syndrome demonstrated mild, patchy podocyte injury, and scattered tubuloreticular inclusions, consistent with minimal change disease with treatment effect (Fig. 3). Although proteinuria initially resolved after 2 weeks of steroid therapy, at 8 months post-biopsy, the patient had experienced one relapse and had nephrotic syndrome (albumin 2.1 g/dL, calculated 24-h proteinuria 4.62 g) at last follow-up.

**Discussion**

We present a multi-institutional cohort of five pediatric patients with COVID-19 and associated kidney dysfunction with available histology. In our series, SARS-CoV-2 infection in children ranged from clinically asymptomatic to severe with MIS-C and ARDS. Kidney pathology demonstrated TMA in three patients with AKI requiring hospitalization. Two had nephrotic syndrome, one with immune complex disease (HSP nephritis), and one with a podocytopathy (minimal change disease). This broad spectrum of kidney injury in the setting of COVID-19 is similar to that reported in the adult population [10–12, 14–17]. Within a short follow-up time, one patient died and the remaining four are currently being treated and have not returned to baseline kidney function.

Three patients with current or prior COVID-19 presented with AKI and systemic features of acute endothelial injury in the spectrum of HUS or DIC. Neither of the two tested patients had underlying abnormalities of the alternative complement pathway. The first (case 1) experienced COVID-19-related ARDS and DIC in the setting of new onset DKA. DKA is known to be precipitated by infections, and COVID-19 represents an additional infection to consider in newly diagnosed diabetics presenting with DKA. At least one had another reason for TMA (STEC HUS, case 2), but given the concurrent SARS-CoV-2 infection, MIS-C, and extensive renal cortical necrosis with resultant chronic kidney disease stage 5, COVID-19 was considered a likely contributor to the severity of the TMA and clinical course [5, 18, 19]. COVID-19-associated TMA has been described in pediatric patients [19], including at least one patient with a kidney biopsy who had MIS-C with coronary artery dilatation (“Kawasaki-like” disease), similar to ours [5]. The third (case 3) had no definitive etiology (Shiga toxin negative diarrhea); although COVID-19 antibodies were detected at presentation, the timing of prior SARS-CoV-2 infection was unknown. Given the presence of COVID-19 antibodies and reports of TMA after SARS-CoV-2 infection in children [5, 19] and adults [10, 14], this represents a potential but unproven trigger for TMA. There is uncertainty as to whether SARS-CoV-2 is a cause of, or contributor to, TMA in these three cases, particularly cases 2 and 3. These cases and their complexity bear similarities to adult series of TMA in the setting of COVID-19, which have been reported predominantly in patients with underlying conditions and are likely mediated by multifactorial endothelial injury [20, 21]. Future studies may help elucidate associations and biologic mechanisms determining development of TMA in children with SARS-CoV-2 infection.

Two previously healthy patients presented with nephrotic syndrome shortly after SARS-CoV-2 infection: one had HSP nephritis/IgA vasculitis, and one had minimal change disease. Both of these biopsies contained endothelial tubuloreticular inclusions, a recognized morphologic manifestation of a high-interferon state seen in the setting of COVID-19 and other viral and autoimmune diseases, particularly untreated hepatitis B or C (HBV, HCV), human immunodeficiency virus (HIV), and lupus. Pediatric IgA vasculitis after COVID-19 has been described in at least 3 case reports [6, 7, 22]. Notably,
post-COVID-19 IgA nephropathy/vasculitis is comparatively under-reported in adult kidney histology-based case series, in which the most common glomerular finding is collapsing glomerulopathy—usually associated with APOL1 high-risk alleles—in addition to acute tubular injury [12]. However, clinically apparent and biopsy-proven flares of IgA nephropathy and IgA vasculitis have been described in adults after SARS-CoV-2 mRNA vaccination [23–26], suggesting an immunologic connection between SARS-CoV-2 and IgA nephropathy/vasculitis in both adults and children, which deserves further study. Similar to our case, post-COVID-19, steroid-responsive nephrotic syndrome consistent with minimal change disease has also previously been reported in a 5-year-old girl (not biopsied) [27], and relapse of nephrotic syndrome after COVID-19 has also been reported [28]. This highlights the apparent podocytopathic effects of SARS-CoV-2 in addition to its known endothelial tropism and capacity for systemic immune activation.

In addition to kidney biopsy findings seen in our series, post-COVID-19 tubulointerstitial nephritis in two children [6] including one with uveitis (TINU) [29] has previously been reported. COVID-19-associated crescentic glomerulonephritis in 2 pediatric patients has also been documented as has de novo collapsing glomerulopathy in a kidney transplant patient [9], but were not present in our cohort. Kidney injury and biopsy findings following COVID-19 infection in children and adolescents have recently been reviewed elsewhere [30]. The proposed mechanisms of COVID-19-associated kidney injury include immune system dysregulation, cytokine activation, dysfunction of coagulation, complement of the microcirculatory system, and some pathophysiology shared with sepsis-associated AKI [31–34]. In our cohort, two patients (cases 1 and 2) presented acutely, and their AKI and TMA were likely driven by more than one of these proposed mechanisms. Three patients (cases 3, 4, and 5) experienced only mild COVID-19 symptoms which preceded kidney dysfunction, suggesting that SARS-CoV-2 infection could have precipitated subsequent immune dysregulation, albeit with morphologically diverse manifestations.

**Conclusion**

In summary, we describe five pediatric patients with COVID-19-associated kidney dysfunction, manifesting as TMA, HSP nephritis/IgA vasculitis, and minimal change disease. Although uncommon, COVID-19-associated kidney injury can have significant morbidity in the unvaccinated pediatric and adolescent population.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s00467-022-05457-w.

**Declarations**

**Ethics approval** This study is approved by our Institutional Review Board (IRB).

**Consent to participate** Not applicable.

**Consent for publication** Not applicable.

**Conflict of interest** The authors declare no competing interests.

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