New-Onset Nephrotic Syndrome with Concurrent COVID-19 Infection in a Pediatric Patient

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Abstract

Minimal change nephrotic syndrome (MCNS) is more common among children. However, there is limited literature associating MCNS and COVID-19 infection. We present a 2 year old boy with anasarca who tested positive for COVID-19 prior to admission. Workup was consistent with nephrotic syndrome. He responded well to steroids and diuretics.

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Marvin Mata - Oversaw the patient's admission, diagnosis, and therapeutic plans of management. Provided the idea for the case report. Provided the initial literature search and synopses of journals. Supervised the draft and revisions for important intellectual content. Gave the final approval of the version of the article to be published.

Christina Rubio - Obtained the patient's medical record from the tertiary facility. Performed literature search. Contributed to the abstract, introduction, case presentation and conclusion.

SaiSwetha Narla - Obtained parental consent for the case report. Performed literature search. Contributed to the case presentation and discussion of the case report.

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Abstract

COVID-19 infections involving renal diseases are more common in adults than children, between 36.6% to 40% of hospitalized patients[1] leading to fatal outcomes in 35 to 36% of cases[2]. Minimal change nephrotic syndrome (NS) is commonly associated with the pediatric population. However, there is limited literature concerning the association between concurrent NS and COVID-19 infection.

We present the case of a previously healthy 2 year old Caucasian male who was referred for admission in August 2022 due to worsening new onset periorbital edema, abdominal distention, and bilateral edema of the extremities. History showed initial symptoms of intermittent low-grade fever followed by right eye swelling. He was initially treated for cellulitis with no improvement. The patient on follow-up tested positive for COVID-19 infection two days before getting admitted. Due to the persistence of symptoms and progression of swelling from facial swelling to abdominal distention and pitting edema of the extremities, he was referred for admission.

The workup done showed findings consistent with nephrotic syndrome including edema, nephrotic range proteinuria, hypoalbuminemia, and hyperlipidemia. The patient responded well to steroid and diuretic

treatment. No complications were noted associated with hypercoagulability, spontaneous bacterial peritonitis, or the development of end-stage renal disease. The patient achieved complete remission within one week of treatment and continues to do so on follow-up with Pediatric Nephrology service.

This report highlights a unique case of nephrotic syndrome in a child with a concurrent COVID-19 infection.

Keywords: pediatric nephrotic syndrome, nephrotic range proteinuria, Covid-19, steroid treatment

Introduction :

The spread of the COVID-19 infection is one of the most significant pandemics of the twenty-first century. It has and continues to pose an enormous burden on the United States healthcare system, with over 99,705,095 total accumulated cases[3]. It exhausted tremendous resources resulting in bed shortage, staff burnout, inability to perform elective surgical cases, inadequate health maintenance, and most importantly, an estimated 921,000 deaths mainly among the adults[3]. Children have continued to show lower risk of infection when compared to adults. As of December 8, 2022, there were only 18% of the total cases reported[4], 3.55% that required hospitalization[4], and only 0.9 deaths per 100,000 cases among children 0 to 17 years of age[5]. In both populations, COVID-19 manifests predominantly with respiratory symptoms such as cough (38.5%) and dyspnea (26.1%)[6]together with fever (81.2%)[7].

Among children, the infection has been less severe and can present with some unusual manifestations such as urticaria, erythema multiforme, varicella like eruptions, Kawasaki like picture, and the development of multisystem inflammatory syndrome (MIS-C)[8]. There has also been increasing literature on COVID-19 and the development of multiorgan dysfunction involving the cardiovascular, central nervous system, gastrointestinal tract, and the kidneys. Strong predictors of renal injury are patient comorbidities like hypertension, diabetes, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), and malignancy but are more common in adults[2]. Kidney involvement, however, occurs in only 10-15% among children[9] and ranges from mild proteinuria and hematuria to acute kidney injury leading to renal failure and the need for renal replacement therapy.

A few cases have resulted in nephrotic range proteinuria in the setting of a concurrent COVID-19 infection. Currently, there are only three cases reported previously. The first is on an 8 year old boy who presented with bilateral eyelid and facial swelling a week before he tested positive for COVID-19. He was asymptomatic except for gastrointestinal symptom of diarrhea[10]. The second is a 15 year old boy who presented with fever, anasarca, myalgia, and oliguria. Work up was positive for COVID-19 and nephrotic range proteinuria consistent with nephrotic syndrome[11]. The third case is a 5 year old with a presentation similar to the first starting with periorbital edema and asymptomatic COVID-19 infection[12]. All three cases showed no prior history of renal disease raising the possibility of an association between NS and COVID-19 as a possible viral trigger.

Some of the other viruses associated with glomerulopathy include respiratory syncytial virus, influenza, parainfluenza, adenovirus, varicella, and cytomegalovirus. Dossier et al. (2014) noted a significant prevalence of herpesviruses (EBV and HHV-7) infection or reactivation in pediatric patients at onset of NS compared to a control[13].

This report is only the fourth case of new onset NS associated with COVID-19 infection out of 17,946,927 total reported cases[4] among children.

Case Description

The patient is a previously healthy 2 year old Caucasian male referred for admission under the pediatric hospitalist service due to swelling of the face, abdomen, and the extremities. History showed initial symptoms of low-grade fever occurring intermittently for a week together with right eye swelling. Upon presentation to his primary care provider, it was treated as cellulitis with Amoxicillin-clavulanate however no improvement was noted. The patient on follow-up after 2 days tested positive for COVID-19 infection. Due to non-response and progression of swelling to both legs, the patient was started on oral prednisolone for possible

allergy and referred to an allergy specialist. His symptoms persisted and on the day of referral was worsened by abdominal distention as noticed by the mother.

Upon admission, vital signs included heart rate of 112 beats per minute, respiratory rate of 24 breaths per minute, blood pressure of 110/78, and oxygen saturation of 96% on room air. Laboratory work up included CBC which showed a white count of 7,600 with hemoglobin of 12.4 g/dL, and hematocrit of 37.3%. Urinalysis on catheterization showed proteinuria >500 mg/dl, moderate blood, and 10-20 RBC/hpf. Metabolic panel showed serum sodium of 136 mmol/L, BUN of 10 mg/dL, creatinine of 0.17 mg/dL, hypoalbuminemia with serum albumin of 1.6 g/dL, and elevated urine protein 503 mg/dl and urine creatinine 69.1 mg/dl with a ratio of 7.27. Serum triglyceride and cholesterol were also both elevated at 599 mg/dL and 668 mg/dL, respectively. Complement levels were normal with C3 at 105 mg/dL and C4 of 28 mg/dL.

The clinical and laboratory findings were both consistent and met the criteria for the diagnosis of new onset nephrotic syndrome, which includes edema, nephrotic range proteinuria, hypoalbuminemia, and hyperlipidemia, and The patient was then started on oral prednisolone at 2 mg/kg/day, dietary sodium and fluid restriction, and diuretic therapy with furosemide. Upon consultation with the Pediatric Nephrology service, the patient was transferred to a tertiary children's hospital due to concerns of possible development of complications such as thrombosis related to hypercoagulability and worsening infection from an immunocompromised state. Management at the tertiary facility included IV steroid, diuretics, and oral proton pump inhibitor.

The patient achieved remission with the anasarca significantly improved, resolution of proteinuria with negative urine protein and urine to protein to creatinine ratio of 1.2, and the patient's weight back down to 14.5 kg. He continued to follow up with the Pediatric Nephrology service as an outpatient.

Discussion :

It is hypothesized that the pathology due to COVID-19 may be secondary to the SARS-CoV and SARS-CoV-2 ability to conjugate with angiotensin-converting enzyme 2 (ACE2) receptors in lung epithelium thereby replicating and downregulating these receptors. The resulting diminished ability to degrade angiotensin II (ATII) results in an upsurge of ATII leading to systemic inflammation. The effects include vasodilation, thrombosis, and further inflammation in multiple organs with ACE2 receptors including the kidneys[14].

Renal features of adults with COVID-19 infection include nephropathy, thrombotic microangiopathy, acute kidney injury, and acute tubular necrosis[2,15]. Histopathologically, podocytopathy and collapsing glomerulopathy are two of the most common findings with African ancestry being a significant demographic factor[16]. Anandh and Bannur (2022) also described its possible immunomodulatory effects in a case series of 3 adult patients who developed nephrotic syndrome four to six weeks post COVID-19 infection with findings of two being steroid responsive while the third did not achieve full remission with steroids but responded well to tacrolimus[17].

Currently there are no studies that provide a direct correlation between COVID-19 and new onset of NS. However, there are some reports on COVID-19 infection causing worsening renal function in patients with CKD. Melgosa (2020) described 16 children with CKD where COVID-19 infection caused worsening of GFR in three, and relapse in two children with steroid dependent nephrotic syndrome[18]. In a case series reported on 186 pediatric patients with Multisystem Inflammatory Syndrome in Children (MIS-C), 92% of the patients had four or more laboratory markers such as elevated erythrocyte sedimentation rate, lymphocytopenia, neutrophilia, hypoalbuminemia, elevated ferritin etc. Hypoalbuminemia was a laboratory finding in almost half of the cases[19]. Basiratnia et al. (2021) described two cases, a 16 and 17 year old, both males, with acute necrotizing glomerulonephritis in the context of COVID-19 infection. Both reported cases underwent hemodialysis; however, the case with more chronic features, which included interstitial fibrosis, arteriolar wall thickening, and fibrinoid necrosis on kidney biopsy progressed to kidney failure while the other responded well to glucocorticoid therapy[20]. In existing pediatric literature on MIS-C in the United States, renal involvement of any kind has been reported in 3-13% and 2-8% is manifested as Acute Kidney Injury (AKI)[20]. AKI remains the most encountered renal manifestation of COVID-19.

Among children, reports of nephrotic range proteinuria as a complication of COVID-19 are minimal. To our knowledge, this is only the fourth pediatric case reporting new onset NS during a COVID-19 infection. Similar to the three previously published case reports, our patient presented with concurrent positive PCR test for COVID-19 and symptoms of NS such as periorbital edema that progressed to include the abdomen and extremities. The patient showed significant response to steroid treatment with improvement of proteinuria and edema.

This report adds to the limited literature on pediatric nephrotic syndrome in association with a COVID-19 infection. It will help provide a better understanding on the course of the disease, response to steroid treatment, and the risk of developing complications, if any, such as end stage renal disease. The patient in this case showed a steroid responsive course similar to the three children previously reported.

Conclusion:

While this case was treated successfully without complications, it serves as an addition to the literature describing the clinical features of children who developed NS in the setting of a COVID-19. This will help medical providers in the management and future prognostication of the disease. This case additionally can serve as a basis for case control studies assessing whether COVID-19 infection (exposure) is a risk factor for the development of new onset or relapse of nephrotic syndrome (outcome) in children. To date, this is only the fourth pediatric case report on a new onset NS associated with a COVID-19 infection.

Reference

1. Hirsch JS, Ng JH, Ross DW, et al. Acute kidney injury in patients hospitalized with COVID-19. *Kidney Int.* 2020;98(1):209-218. doi:10.1016/j.kint.2020.05.006 2. Cheng Y, Luo R, Wang K, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney Int.* 2020;97(5):829-838. doi:10.1016/j.kint.2020.03.005 3. Estimated Covid-19 burden. Centers for Disease Control and Prevention (CDC). Updated August 12, 2022. Accessed December 22, 2022. https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/burden.html 4. Children and covid-19: state-level report. American Academy of Pediatrics. Updated December 22, 2022.. Accessed December 22, 2022. https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and -covid-19-state-level-data-report/ 5. Covid Data Tracker. Centers for Disease Control and Prevention.Updated December 22, 2022. Covid data tracker. Accessed December 17, 2022. https://covid.cdc.gov/covid-data-tracker/#datatracker-home 6. Alimohamadi Y, Sepandi M, Taghdir M, Hosamirudsari H. Determine the most common clinical symptoms in COVID-19 patients: a systematic review and meta-analysis. *J Prev Med Hyg.* 2020;61(3):E304-E312. Published 2020 Oct 6. doi:10.15167/2421-4248/jpmh2020.61.3.1530 7. Chao JY, Derespina KR, Herold BC, et al. Clinical Characteristics and Outcomes of Hospitalized and Critically Ill Children and Adolescents with Coronavirus Disease 2019 at a Tertiary Care Medical Center in New York City. *J Pediatr.* 2020;223:14-19.e2. doi:10.1016/j.jpeds.2020.05.006 8. Colonna C, Restano L, Monzani N, et al. Rare and common manifestations of COVID-19 in children. *JEADV Clinical Practice.* 2022;1(1):21-30. doi:10.1002/jvc2.10 9. Mittal A, Nadig P, Singh K. Renal manifestations of COVID 19 in children. *J Family Med Prim Care.* 2022;11(6):2302-2310. doi:10.4103/jfmpc.jfmpc_1777_21 10. Shah SA, Carter HP. New-Onset Nephrotic Syndrome in a Child Associated With COVID-19 Infection. *Front Pediatr.* 2020;8:471. Published 2020 Aug 20. doi:10.3389/fped.2020.00471 11. Alvarado A, Franceschi G, Resplandor E, Sumba J, Orta N. COVID-19 associated with onset nephrotic syndrome in a pediatric patient: coincidence or related conditions?. *Pediatr Nephrol.* 2021;36(1):205-207. doi:10.1007/s00467-020-04724-y 12. Morgan KM, Imani PD. Case report: a 5-year-old with new onset nephrotic syndrome in the setting of COVID-19 infection. *BMC Nephrol.* 2021;22(1):323. Published 2021 Sep 27. doi:10.1186/s12882-021-02520-w 13. Dossier C, Sellier-Leclerc AL, Rousseau A, et al. Prevalence of herpesviruses at onset of idiopathic nephrotic syndrome. *Pediatr Nephrol.* 2014;29(12):2325-2331. doi:10.1007/s00467-014-2860-1 14. Shirbhate E, Pandey J, Patel VK, et al. Understanding the role of ACE-2 receptor in pathogenesis of COVID-19 disease: a potential approach for therapeutic intervention.*Pharmacol Rep.* 2021;73(6):1539-1550. doi:10.1007/s43440-021-00303-6 15. Cancarevic I, Nassar M, Medina L, et al. Nephrotic Syndrome in Adult Patients With COVID-19 Infection or Post COVID-19 Vaccine: A Systematic Review.*Cureus.* 2022;14(9):e29613. Pub-

lished 2022 Sep 26. doi:10.7759/cureus.29613 16. Shetty AA, Tawhari I, Safar-Boueri L, et al. COVID-19-Associated Glomerular Disease.*J Am Soc Nephrol*. 2021;32(1):33-40. doi:10.1681/ASN.2020060804 17. Anandh U, Bannur S. Nephrotic Syndrome Post COVID 19 Infection: Association or Mere Coincidence? *Annals of Case Reports*. 2022;7(3). doi:10.29011/2574-7754.100842 18. Melgosa M, Madrid A, Alvárez O, et al. SARS-CoV-2 infection in Spanish children with chronic kidney pathologies. *Pediatr Nephrol*. 2020;35(8):1521-1524. doi:10.1007/s00467-020-04597-1 19. Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. *N Engl J Med*. 2020;383(4):334-346. doi:10.1056/NEJMoa2021680 20. Basiratnia M, Derakhshan D, Yeganeh BS, Derakhshan A. Acute necrotizing glomerulonephritis associated with COVID-19 infection: report of two pediatric cases.*Pediatr Nephrol*. 2021;36(4):1019-1023. doi:10.1007/s00467-021-04944-w