

Renal failure in a pediatric patient secondary to HCoV-NL63 infection: A case report

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ABSTRACT

Background: Coronaviruses (CoVs) are members of the Nidovirales family, Coronaviridae. To date, seven human CoVs have been identified, some of which are known to circulate persistently in the human population, particularly among young infants. Among these CoV types, renal disease is a recognized complication associated with SARS-CoV-2. No cases of renal disease caused by HCoV-NL63 have been reported. **Case report:** A 4-year-old girl presented with severe renal injury and cardiorespiratory collapse as a result of HCoV-NL63-associated glomerulonephritis. Histopathology from a renal biopsy revealed severe tubulointerstitial changes. She was subsequently placed on continuous ambulatory peritoneal dialysis (CAPD) with a Tenckhoff catheter as a long-term renal replacement therapy due to her incomplete recovery. **Conclusion:** HCoV-NL63, previously identified as causing moderate respiratory symptoms in infants, is capable of inducing severe renal impairment in childhood. Histopathological findings in the renal area are critical in determining the pathology of this rare etiology that causes childhood glomerulonephritis. This report emphasizes the novelty and importance of this rare case in pediatric nephrology.

Key words: Coronavirus, Glomerulonephritis, Paediatric

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INTRODUCTION

Coronaviruses (CoVs) are members of the Nidovirales family, within the Coronaviridae subfamily. CoVs are positive-strand RNA viruses with large genomes ranging in size from 27 to 33 kb¹. To date, seven human CoVs have been identified, some of which persistently circulate in the human population, particularly among young infants. Initially detected in the mid-1960s, HCoV-229E and HCoV-OC43 have been associated with the common cold and, in rare cases, with lower respiratory tract infections². In 2003, a third human coronavirus (SARS-CoV) was identified as the causative agent of severe acute respiratory syndrome (SARS)¹. HCoV-NL63 and HCoV-HKU1 were two additional human coronaviruses identified after 2003¹. The Middle East respiratory syndrome coronavirus (MERS-CoV) emerged in the Arabian Peninsula in 2012 as a highly lethal human pathogen². The novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), was discovered in Wuhan, China, in 2019 and has since caused a global pandemic³. Among these CoV types, renal disease has been recognized as a complication associated with SARS-CoV-2, as previously reported by Lv W *et al.*². Specific studies directly correlating HCoV-NL63 with renal impairment in pediatric patients are limited. While some children

with HCoV-NL63 infections have underlying health issues, including renal problems, the majority of research focuses on respiratory outcomes, and the direct causative relationship remains to be established. We present the case of a 4-year-old girl who presented with severe renal injury and cardiorespiratory collapse as a result of HCoV-NL63-associated glomerulonephritis. We have reviewed the associated pathology of the underlying disease.

METHODS

A 4-year-old girl presented with a sudden onset of cardiorespiratory collapse following a 2-day history of cough, coryza, loose stools, and vomiting. The patient exhibited severe acute renal injury (ARI) and hepatorenal syndrome, complicating her condition. She was ventilated due to respiratory failure and hemodynamic instability. She had anuric renal failure and received continuous veno-venous hemofiltration (CVVH) via a right internal jugular vein catheter for five days.

On examination, she was not syndromic, being short and slender (with both weight and height below the 3rd percentile). She appeared sallow and was not edematous. She was afebrile and hypertensive, with a pulse rate of 100 beats per minute and a blood pressure of 160/100 mmHg. Her skin was dry, with scabs from a previous skin infection covering her

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body. Lung auscultation revealed diminished breath sounds bilaterally. The remaining systemic examinations were inconclusive.

Table 1 shows that a creatinine level of 1467 $\mu\text{mol/L}$ and an estimated glomerular filtration rate (eGFR) of 2.5 ml/min/1.73 m^2 indicated renal impairment. Urine analysis revealed hematuria and proteinuria, with red blood cell (RBC) and protein levels of 3+, respectively. The peripheral blood film demonstrated a leukoerythroblastic pattern accompanied by neutrophilia and left-shifted red blood cell alterations, all indicative of infection. The results of all autoantibody assays were negative. HCoV-NL63 was identified as the respiratory pathogen by rapid molecular detection. A chest radiograph showed left pleural effusion and right loculated pneumothorax, for which a left-sided chest tube was inserted. Pleural fluid examination revealed an exudative type with no positive culture. Abdominal and kidney-ureter-bladder (KUB) ultrasounds indicated bilateral renal and liver parenchymal disease. Brain computed tomography (CT) revealed no abnormalities. Because of the lack of improvement in renal function despite consistent hemodialysis, a renal biopsy was performed on the patient's left kidney. Histopathological (HPE) analysis of the kidney biopsy indicated that, of the 60 glomeruli examined, 55 showed global sclerosis, and only five remained viable (**Figure 1**). Active lesions, including crescent formation, endocapillary hypercellularity, and necrotizing lesions, were not observed. Tubular atrophy and interstitial fibrosis, comprising moderate to severe chronic tubulointerstitial changes, were observed in over 50% of the biopsy with diffuse acute tubular injury changes. Moderate chronic vascular changes were noted in the vessels, manifesting as fibro-myxoid changes and thickened wall thickness. Immunohistochemistry stains for CD61 indicated the existence of fibrin thrombi within the vessels' lumen. She received 30 mg/kg body weight of intravenous (IV) methylprednisolone per day for three days. An angiotensin-converting enzyme inhibitor, a beta-blocker, and a calcium channel blocker were administered to regulate her blood pressure. In addition to packed cell transfusions administered during hemodialysis, the patient underwent intravenous infusions of iron sucrose to treat her anemia. The patient's renal function did not fully recover, necessitating renal replacement therapy (RRT). Given the challenges with accessing veins and the cost-effectiveness of the option, she was transitioned to continuous ambulatory peritoneal dialysis (CAPD) using a Tenckhoff catheter as her long-term RRT.

DISCUSSION

HCoV-NL63 is the fifth discovered human coronavirus and, unlike SARS-CoV-2, it produces mild respiratory illnesses in infants¹. Researchers in Amsterdam initially identified HCoV-NL63 in 2004 from a nasopharyngeal aspirate of a seven-month-old infant⁴. The existing literature provides limited information regarding its association with severe renal manifestations. In this case, the most plausible pathogenic etiology of the renal impairment was glomerulonephritis caused by HCoV-NL63. Given the patient's abrupt onset of acute kidney injury (AKI) and histopathological examination (HPE) analysis, the most plausible diagnosis is rapidly progressive glomerulonephritis (RPGN), potentially caused by HCoV-NL63. RPGN is marked by a sudden loss of renal function over days or weeks, evident in the urine (proteinuria, micro, or macroscopic hematuria, dysmorphic red blood cells (RBC), RBC casts), and also in the kidneys' histopathological features of crescentic glomeruli⁵. Without treatment, RPGN can advance to renal failure within weeks or months. Consequently, immediate treatment is essential, consisting of at least three doses of pulsed IV methylprednisolone and plasmapheresis⁵.

Three of these coronaviruses, namely COVID-19, SARS, and MERS, have spread and caused exceptionally hazardous diseases⁴. The remaining four, HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1, are mildly pathogenic and induce just common cold symptoms in immunocompetent persons⁴. Patients infected with SARS-CoV, MERS-CoV, or SARS-CoV-2 may present with acute respiratory illness (ARI), although retrospective studies have not consistently reported the incidence of ARI. They hypothesize that a pro-inflammatory cytokine response or viral replication-mediated renal cytopathy could directly or indirectly induce ARI based on their analysis of ARI reports associated with SARS-CoV, MERS-CoV, and SARS-CoV-2 infections². Lednicky et al. discovered HCoV-NL63 in commercially available primary human renal proximal tubule epithelial cells (RPTEC)⁶ and subsequently demonstrated that the virus replicates in primary human kidney cells at high titers⁶. Despite its classification as a respiratory virus with moderate virulence, HCoV-NL63 has not been associated with renal disease in humans⁶. SARS and MERS coronaviruses, on the other hand, are genetically related and are responsible for inducing severe respiratory and renal diseases³. This leads to an inquiry into whether HCoV-NL63 impacts the kidneys. Previous studies have linked SARS-CoV, which possesses the identical ACE2 receptor as HCoV-NL63, to

Table 1: Laboratory investigations

	27/5/23	10/6/23	13/6/23	15/6/23	23/6/23
WBC ($10^9/L$)	16.4	30.28	15.5	10.28	20.8
Haemoglobin (g/dL)	5.4	12.8	9.9	9.7	9.1
Haematocrit	15.9	38.2	30.9	30.7	27.7
Platelet ($10^9/L$)	250	1097	929	847	728
Sodium	137	140	142	142	138
Potassium	5.2	2.9	3.5	4.9	4.7
Urea	45.9	23	24.4	23	17.3
Creatinine	1467	800	715	496	446
Calcium	1.85	2.45	2.32	2.38	2.17
Phosphate	5.43	1.56	2.19	1.54	1.88
ALP	110	136	108	117	162
Albumin	20	41	32		38
CRP	<5			27.7	
LDH	1892		650		
INR	1.5				0.89
APTT	52.3				37.9
PT	19.7				12.2
C3	0.43				
C4	<0.08				
ANA	Negative				
ASOT	Negative				

WBC: white blood cell; INR: international normalized ratio; [®]ASOT: antistreptolysin O

[‡]ALP: alkaline phosphatase; [‡]APTT: activated partial thromboplastin time

[§]CRP: C-reactive protein; PT: prothrombin time

[‡]LDH: lactate dehydrogenase; [‡]ANA: antinuclear antibody

kidney disease⁶. It is conceivable that HCoV-NL63 is also capable of inducing kidney disease, albeit with considerably less severity compared to SARS-CoV. HCoV-NL63 may contribute to renal impairment by causing direct viral effects on the renal epithelial cells, a systemic inflammatory response, and co-infection with other viruses or bacteria⁷. Given the potential for HCoV-NL63 to contribute to renal impairment, clinicians should be vigilant in monitoring renal function in pediatric patients diagnosed with HCoV-NL63 infections. Despite undergoing dialysis, this patient's kidney function has become irreversible, resulting in a poor prognosis. This patient may be a candidate for a renal transplant, which we need to discuss further with the parents.

CONCLUSION

The case of HCoV-NL63's potential renal impacts serves as a reminder of the need for ongoing research and the development of clinical guidelines that address the multifaceted effects of respiratory viruses in pediatric patients. By enhancing our understanding and management of these infections, we can improve outcomes and the quality of life for affected children.

ABBREVIATIONS

ACE2 - Angiotensin-Converting Enzyme 2, AKI - Acute Kidney Injury, ARI - Acute Renal Injury, CAPD - Continuous Ambulatory Peritoneal Dialysis, CoV - Coronavirus, CoVs - Coronaviruses, COVID-19 - Coronavirus Disease 2019, CT - Computed Tomography, CVVH - Continuous Veno-Venous

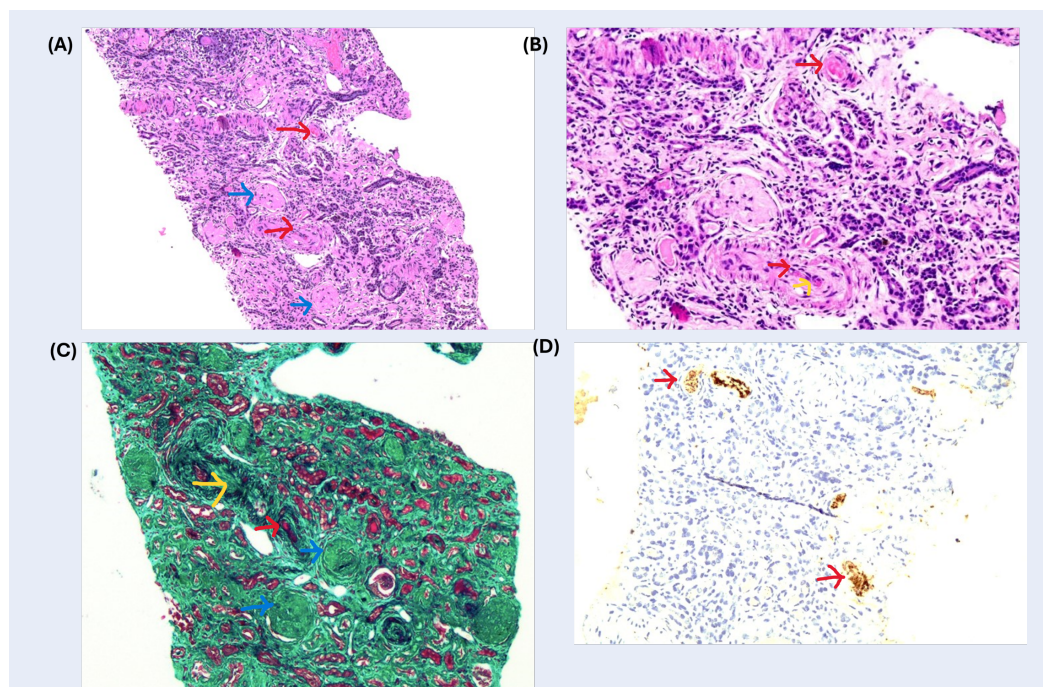


Figure 1: Histopathological analysis of the kidney biopsy. (A) Widespread glomerular ischemia with global sclerosis (blue arrow) associated with thrombotic microangiopathy changes (red arrow) in the background of moderate to severe chronic tubulointerstitial damages (H&E×40); (B) Small artery shows obliterated lumina with fibrin thrombi (red arrow) and mucoid thickening of the intima is seen in the larger artery (yellow arrow (H&E×200); (C) Larger and smaller arteries show moderate to marked intima fibroplasia and medial hypertrophy (yellow arrow) with narrowed lumen and residual fibrin thrombi (red arrow). Widespread globally sclerosed glomeruli are appreciated in the background (blue arrow) (Masson Trichrome ×100); (D) Immunohistochemistry stain for CD61 highlighted the presence of fibrin thrombi within the vessels lumen (red arrow) (CD61: IHC×100). **Abbreviations:** **CD61:** Cluster of Differentiation 61; **H&E:** Hematoxylin and Eosin; **IHC:** Immunohistochemistry

Hemofiltration, **GFR** - Estimated Glomerular Filtration Rate, **HCoV-NL63** - Human Coronavirus NL63, **HPE** - Histopathological Examination, **IV** - Intravenous, **KUB** - Kidney-Ureter-Bladder, **MERS-CoV** - Middle East Respiratory Syndrome Coronavirus, **μmol/L** - Micromoles Per Liter, **RBC** - Red Blood Cells, **RPTEC** - Renal Proximal Tubule Epithelial Cells, **RPGN** - Rapidly Progressive Glomerulonephritis, **RRT** - Renal Replacement Therapy, **SARS-CoV** - Severe Acute Respiratory Syndrome Coronavirus, **SARS-CoV-2** - Severe Acute Respiratory Syndrome Coronavirus 2

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AUTHOR'S CONTRIBUTIONS

AMMK and MII participate in drafting the case report. KI and NACJ creating the outline of the case. All authors read and approved the final manuscript.

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AVAILABILITY OF DATA AND MATERIALS

Data and materials used and/or analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Written informed consent was obtained from the parents of the patient for publication of this Case Report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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