CASE REPORT

Acute tubulointerstitial nephritis in 10-year-old boy following severe acute respiratory syndrome coronavirus 2 infection

Aleksandra Sobieszczańska-Droździel¹, Adam Strzoda², Wojciech Sowiński²

¹Department of Pediatric Nephrology, Medical University of Lublin, Poland
²Student's Scientific Group at the Department of Pediatric Nephrology, Medical University of Lublin, Poland

ABSTRACT

The COVID-19 pandemic caused by coronavirus SARS-CoV-2 is currently a main public health problem worldwide. The clinical symptoms relate primarily to the respiratory system but may also involve multiple organs. The course of COVID-19 in children is usually mild, but in some cases may cause late complications, particularly the pediatric inflammatory multisystem syndrome (PIMS-TS). One of its symptoms may be acute kidney injury.

We present a 10-year-old boy who developed nonspecific symptoms a few weeks after mild COVID-19, including weakness, weight loss, and polyuria. Clinical evaluation revealed acute renal failure secondary to acute tubulointerstitial nephritis (ATIN). Treatment with glucocorticoids resulted in rapid clinical and laboratory improvement. We hypothesize that the development of ATIN could be causally related to COVID-19 in an immune pathomechanism similar to PIMS-TS. The case provides new insights into possible complications of SARS-CoV-2 infection and indicates the need for renal follow-up after COVID-19.

KEY WORDS: COVID-19, acute tubulointerstitial nephritis, PIMS-TS.

INTRODUCTION

A pandemic of coronavirus disease 2019 (COVID-19) caused by the novel coronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), first identified in December 2019 in Wuhan, China, become a main public health problem worldwide. Although COVID-19 is primarily a pulmonary disease, it may involve all other organs and may lead to a fatal outcome. The clinical presentation in children is usually mild or asymptomatic [1-3], however serious post-COVID complications may occur in this age group [4].

We report on a 10-year-old boy who after mild COVID-19 developed acute tubulointerstitial nephritis (ATIN) with renal failure. The clinical course may suggest a causative role of SARS-CoV-2 infection in this process.

CASE REPORT

A 10-year-old boy was referred at the end of December 2020 to our Department shortly after the renal failure of unknown origin was diagnosed at a local hospital. Ten weeks earlier the boy developed mild COVID-19 confirmed by real-time RT-PCR test, presented with short-term fever, sore throat, myalgia, dry cough, and dysgeusia. He was not treated with antibiotics and only twice took a small dose of paracetamol. When within the next few weeks following recovery from acute symptoms, fatigue, decreased appetite, polyuria, and weight loss
TABLE 1. Follow-up of selected laboratory results in the presented patient

| Laboratory parameters | Reference range | Admission (day 0) | Prednisone initiation (day 9) | Follow-up (day 16, prednisone 30 mg/day) | Follow-up (day 33, prednisone 30 mg/day) | Follow-up (day 62, prednisone 10 mg/day) |
|-----------------------|-----------------|------------------|-----------------------------|-----------------------------------------|----------------------------------------|----------------------------------------|
| **Blood**             |                 |                  |                             |                                         |                                        |                                        |
| Urea, mg/dl           | 15-36           | 43.9             | 29.8                        | 46.5                                    | 34.7                                    | 24.5                                    |
| Creatinine, mg/dl     | 0.39-0.73       | 1.31             | 1.26                        | 0.78                                    | 0.64                                    | 0.64                                    |
| Uric acid, mg/dl      | 2.2-5.8         | 3.37             | –                           | –                                       | 2.79                                    | 3.59                                    |
| C-reactive protein mg/dl | 0-0.5          | 4.42             | 2.28                        | 0.45                                    | 0.1                                     | 0.15                                    |
| Procalcitonin, ng/ml  | 0-0.5           | 0.353            | –                           | –                                       | 0.06                                    | 0.058                                   |
| Ferritin ng/ml        | 14-124          | 320.8            | 279                         | 245.7                                   | 103.8                                   | 70.1                                    |
| Erythrocyte Sedimentation Rate, mm/h | 2-15 | 131             | 120                         | 118                                     | 17                                      | 16                                      |
| Troponin I, ng/ml     | <0.16           | <0.1             | <0.1                        | <0.1                                    | <0.1                                    | <0.1                                    |
| pro-BNP, pg/ml        | 0-62            | 209.1            | 884.6                       | 143.1                                   | <10                                     | <10                                     |
| Hematocrit, %         | 35-42.4         | 29.7             | 29.7                        | 31.5                                    | 35.1                                    | 40.9                                    |
| Hemoglobin, g/dl      | 12-14           | 9.6              | 9.7                         | 10.3                                    | 11.7                                    | 13.9                                    |
| MCV, fl               | 76.5-90.6       | 73.6             | 74.1                        | 75                                      | 80.1                                    | 80                                      |
| MCH, pg               | 25-31           | 25.3             | 24.2                        | 24.5                                    | 26.7                                    | 27.2                                    |
| Platelet count, n x 10³ cells/µl | 140-420 | 766             | 679                         | 911                                     | 338                                     | 445                                     |
| Albumin, g/dl         | 3.8-5.4         | 3.9              | 4.23                        | 4.59                                    | 5.06                                    | 5.04                                    |
| Total protein, g/dl   | 6-8             | 8.4              | 9.05                        | 8.82                                    | 7.97                                    | 7.79                                    |
| Alanine aminotransferase, U/l | 0-39   | 8               | –                           | –                                       | 26                                      | 22                                      |
| Immunoglobulin G, mg/dl | 698-1560 | 2013            | 2053                        | –                                       | 1090                                    | 1057                                    |
| Immunoglobulin A, mg/dl | 53-204 | 419             | 386                         | –                                       | 172                                     | 153                                     |
| Complement C3, mg/dl  | 80-150          | 147              | 158                         | –                                       | 124                                     | 138                                     |
| Complement C4, mg/dl  | 12-36           | 35               | 39                          | –                                       | 22                                      | 27                                      |
| Fibrinogen, g/l       | 1.9-4.0         | 6.04             | 5.73                        | 4.12                                    | 2.41                                    | 3.55                                    |
| D-dimers, ng/ml       | <500            | 1084             | 782                         | 431                                     | 366                                     | 354                                     |
| Calcium, mmol/l       | 2.2-2.7         | 2.54             | 2.59                        | 2.63                                    | 2.58                                    | 2.59                                    |
| Phosphates, mmol/l    | 1.05-1.85       | 1.82             | 1.48                        | 1.4                                     | 1.31                                    | 1.56                                    |
| Bicarbonates, mmol/l  | 22.5-30         | 20.5             | 21                          | 21.6                                    | 22.4                                    | 22                                      |
| **Urine**             |                 |                  |                             |                                         |                                        |                                        |
| Specific gravity      | 1.015-1.030     | 1.010            | 1.005                       | 1.010                                   | 1.025                                   | 1.015                                   |
| Glucose, mg/dl        | 0               | 0                | 85                          | 168                                     | 0                                       | 0                                       |
| Protein, mg/dl        | 0-15            | 0                | 0                           | 0                                       | 0                                       | 0                                       |
| pH                    | 5-7             | 5.0              | 6.5                         | 8.0                                     | 6.0                                     | 7.0                                     |
| Erythrocytes n per high power field | 0-5  | 0-1              | 0                           | 0                                       | 0                                       | 0                                       |
| Leukocytes, n per high power field | 0-5  | 3-5              | 0-1                         | 1-3                                     | 2-4                                     | 0-1                                     |
| Uric acid excretion, mg/kg/24 h | 5-15 | –                | –                           | 22.8                                    | 18.63                                   | 18.63                                   |
| Protein excretion, mg/24 h | 0-140 | –                | –                           | <30                                     | <30                                     | <30                                     |

Of about eight kilograms were observed, he was admitted to the local hospital. Laboratory tests showed positive anti-SARS CoV2 antibodies titer (179.4 COI, negative < 1.0), negative SARS-CoV-2 nucleoprotein based antibody test, elevated serum creatinine level (1.4 mg/dl, eGFR 58.3 ml/min/1.73m², estimated with Schwartz formula) with normal urea (42 mg/dl) and relatively low uric acid (3.2 mg/dl) concentrations, increased inflammatory markers (CRP 4.42 mg/dl, ESR 131 mm/h, ferritin 307.71 µg/l), moderate anemia (Hgb 10.3 g/dl,
Acute tubulointerstitial nephritis is a rare cause of AKI in children, accounting for less than 10% of all cases and involving the renal tubulointerstitial tissue with an infiltrate of T-lymphocytes, eosinophils, and monocytes, while glomeruli and vessels are initially unaffected. Since in the majority of cases renal biopsy is not performed, the diagnosis of ATIN as in our patient is made on a clinical basis. Typical features include non-oliguric acute renal failure of various degrees, signs of tubular dysfunction, proteinuria and/or sterile leukocyturia, eosinophilia, increased renal echogenicity in USG, abdominal and/or loin pain, and normal blood pressure [5, 6]. Our patient met most of these criteria, including non-oliguric AKI, renal glycosuria, a tendency to hypouricemia due to hyperuricosuria, decreased serum bicarbonate level, hypostenurinia, clinical symptoms, and typical renal imaging. Due to the patient's stable general condition, lack of progression of renal failure, and a very good response to steroid treatment we abandoned the initially planned kidney biopsy.

Acute tubulointerstitial nephritis is usually caused by hypersensitivity reactions to medications, toxins, autoimmune disorders, or infections. As these three former reasons may be rather excluded in our patient by his medical history and laboratory results, the only possible detectable factor remained SARS-CoV-2 infection.

It is well known that different microorganisms, including viruses and bacteria, may be responsible for the devel-

![Image](image_url)
opment of ATIN. Viral and bacterial antigens may initiate cell-mediated injury due to delayed idiosyncratic hypersensitivity immune reactions. The antigens are filtered, concentrated, and secreted within the kidneys what along with high blood flow, increases their exposure and makes them a target of immunological reactions [5, 6]. Respiratory viruses can trigger Kawasaki disease [7] while bacterial superantigens of either Staphylococcus aureus or Streptococcus pyogenes may cause toxic shock syndrome [8].

Acute kidney injury is the most common renal manifestation in COVID-19 patients, reported in around 3-9% of them [9], but its incidence is much higher among those who require hospitalization [10]. The pathomechanism is not fully understood but it may be related to direct renal tropism of SARS-CoV-2 or indirect effects resulting from systemic consequences of COVID-19 [11]. The former is possible, as SARS-CoV-2 cellular membrane receptors – ACE2 are expressed in renal proximal tubular cells, podocytes, and glomerular visceral epithelial cells. It was confirmed by the presence of SARS-CoV-2 RNA in the damaged tubular epithelium [9]. Indirect mechanisms of AKI include renal hypoperfusion due to hypovolemia, cytokine storm, microvascular thrombosis, or side effects of intensive treatment [12]. Interestingly, to date, only one case of biopsy-proven ATIN with COVID-19 and AKI was reported [13].

Specifically, in children AKI related to COVID-19 may be a part of pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) [4, 14]. This serious condition usually occurs 2-6 weeks after COVID-19 as severe hyperinflammation leading to multisystemic manifestation. It is characterized by a broad spectrum of symptoms, including fever, myalgia, myocarditis, coronary aneurysms, gastroenteritis, lymphadenopathy, skin rash, stomatitis, conjunctivitis, central neuropathy, pneumonia, elevated markers of inflammation, and renal failure. Although precise pathomechanism of PIMS-TS is not fully understood, it is considered as a post-viral abnormal immunological reaction [4, 15].

Obviously, the presented patient did not meet the diagnostic criteria of PIMS-TS. However, we cannot exclude the immunological mechanism of ATIN in this case. Similarly to PIMS-TS, our patient developed a systemic inflammatory reaction confirmed by elevated CRP, ESR, ferritin, fibrinogen, D-dimer levels, as well as hypergammaglobulinemia. It may be responsible for his general symptoms, including malaise and severe weight loss several weeks before clinical evaluation. If kidneys and other organs were involved in this process during this time, remains speculative. Finally, the rapid response to corticosteroids may also support our hypothesis.

CONCLUSIONS

The presented case shows a possible complication of SARS-CoV-2 infection and provides new insights into the clinical spectrum of COVID-19. We hypothesize that the development of ATIN after COVID-19 may represent a milder form of PIMS-TS, which in some cases may be overlooked. Therefore, a follow-up of pediatric cases with prior COVID-19, regardless of its severity, should be warranted.

DISCLOSURE

The authors declare no conflict of interest.

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