An Unusual Presentation of Pyelonephritis: Is it COVID-19 Related?

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Research Article

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Abstract

Introduction

In severe cases of COVID-19, late complications such as coagulopathy and organ injury are increasingly described. In milder cases of the disease, the exact time frame and causal path of late onset complications has not yet been determined. Although direct and indirect renal injury by SARS-CoV-2 has been confirmed, hemorrhagic renal infection or coagulative problems in the urinary tract have not yet been described.

Case Presentation

This case report describes a 35-year-old female without relevant medical history who, five days after having recovered from an infection with SARS-CoV-2, had an unusual course of acute pyelonephritis of the right kidney and persistent fever under targeted antibiotic treatment. A hemorrhagic ureteral obstruction and severe swollen renal parenchyma preceded the onset of fever and was related to the developing pyelonephritis. Sudden thrombotic vascular occlusion in the right eye appeared during admission. Symmetrical paresthesia in the limbs in combination of severe lower back pain and gastrointestinal manifestation was documented and not been explained despite of intensive investigation.

Conclusion

We present the unusual combination of culture confirmed bacterial hemorrhagic pyelonephritis with a blood clot in the proximal right ureter, complicated by a retinal venous thrombosis, in a patient who had recovered from SARS-CoV-2-infection five days before presentation. The case is suspect of a COVID-19 related etiology.

Introduction

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), recognized as pandemic by the WHO in March 2020, has presented increasing challenges for healthcare professionals and societies. Although the understanding of the associated Coronavirus disease 19 (COVID-19) is rapidly evolving, the clinical manifestation and consequences remain to be fully delineated.

While respiratory symptoms are the most apparent features of the disease, endothelial dysfunction, abnormal coagulation parameters and consecutive thrombosis are increasingly recognized sequelae [1, 2]. Complications that stem from such vascular aberrations occur in up to 31% of ICU patients with COVID-19 [2]. Acute kidney injury is also a common characteristic of hospitalized patients with severe COVID-19 infection [1, 3]. Although such renal injury through systemic illness, sepsis, vascular occlusion and even direct viral damage of the nephron are increasingly documented, pyelonephritis and ureteral complications have not yet been reported in relationship to a SARS-COV-2 infection [3–5].
We present a case of a 35-year-old female without comorbidity, who, five days after recovering from COVID-19, had an unusual course of acute bacterial pyelonephritis, hemorrhagic ureteral obstruction and persistent fever despite antibiotic treatment. Her course of disease was further complicated by venous retinal thrombosis.

Case Presentation

A 35-year-old female presented to the emergency room with acute constant right sided flank pain, urge to move, vomiting, and macroscopic hematuria with blood clots for three days. Two weeks earlier, she had been diagnosed with COVID-19, following a transient fever and loss of smell and taste till five days before presentation. At presentation, the patient did not have raised temperature or any urinary tract-, gastrointestinal-, or cardiopulmonary symptoms. Her medical history was unremarkable except for two episodes of pyelonephritis (side unknown), one during pregnancy, of which she clearly recognized the pain. She did not use any medication.

Vital functions and physical examination showed no abnormalities. Blood tests revealed a serum creatinine level of 65 µmol/L, with an eGFR (MDRD) of 90 ml/min/1.73m^2. Leucocytes were elevated (13.5 x10^9/L, Table 1). Urine was positive for erythrocytes, leukocytes and nitrites. Ultrasound showed hydronephrosis of the right kidney. Enhanced computed tomography (CT) revealed an obstructive dense mass of 75HU, corresponding with a blood clot, in the proximal right ureter close to the renal pelvis. The right kidney showed severe parenchymal thickening, multiple small calcifications deep in the calyces and extensive hydronephrosis (Fig. 1). In addition, ground glass opacities were observed in the peripheral basal lung area's; suspect for remnants of the SARS-CoV-2 infection.
| Test                                      | Range          | At first presentation (29-07-2020) | At start of fever (01-08-2020) | 5 days before discharge |
|-------------------------------------------|----------------|------------------------------------|---------------------------------|------------------------|
| Urea, mmol/L                              | 2.5–7.5        | 3.7                                | 6.1                             |                        |
| Creatinine, µmol/L                        | 50–95          | 65                                 | 113                             | 57                     |
| estimated GFR (CKD-EPI), ml/min/1.73m²    | >83            | 106                                | 55                              | 116                    |
| Calcium, mmol/L                           | 2.15–2.55      | 2.30                               |                                 |                        |
| Sodium, mmol/L                            | 135–145        | 134                                | 134                             |                        |
| Potassium (plasma), mmol/L                | 3.2–4.7        | 3.7                                | 4.0                             | 4.1                    |
| Chloride, mmol/L                          | 97–107         | 102                                |                                 |                        |
| ASAT, U/L                                 | <30            | 23                                 | 25                              |                        |
| ALAT, U/L                                 | <34            | 9                                  | 19                              |                        |
| LD, U/L                                   | <248           | 183                                | 254                             |                        |
| GGT, U/L                                  | <40            | 11                                 | 12                              |                        |
| Bilirubin, total, µmol/L                  | 5–19           | 9                                  | 7                               |                        |
| Alkaline Phosphatase, U/L                 | 40–120         | 66                                 | 90                              |                        |
| Total protein, g/L                        | 63–83          | 75                                 |                                 |                        |
| Albumin, g/L                              | 32–48          | 42                                 |                                 |                        |
| CK, U/L                                   | 10–145         | 48                                 |                                 |                        |
| NT-proBNP (ng/l)                           | <125           | 93                                 |                                 |                        |
| Hemoglobin (mmol/L)                       | 7.2–9.5        | 8.6                                | 6.4                             |                        |
| Hematocrit (L/L)                          | 0.36–0.47      | 0.42                               | 0.32                            |                        |
| Erythrocytes (x10^12/L)                   | 4.0–5.3        | 5.1                                | 3.8                             |                        |
| Test                     | Range    | At first presentation (29-07-2020) | At start of fever (01-08-2020) | 5 days before discharge |
|-------------------------|----------|------------------------------------|--------------------------------|------------------------|
| MCV (fL)                | 83–100   | 83                                 | 82                             |                        |
| Trombocytes (x10^9/L)   | 150–400  | 322                                | 119                            |                        |
| Leucocytes (x10^9/L)    | 4.0–10.0 | 13.5                               | 13.9                           |                        |
| CRP (mg/L)              | < 0.5    | 3                                  | 246                            | 27                     |
| Glucose (mmol/L)        | 3.5–9.0  | 5.6                                |                                |                        |
| Protrombin time (sec)   | 9–12     | 10.1                               |                                |                        |
| APTT (sec)              | 24–33    | 29                                 |                                |                        |
| D-dimer (mg/L)          | < 0.5    | 0.49                               |                                |                        |
| Ferritin (ug/L)         | 10–100   | 92                                 |                                |                        |

The patient was admitted to the hospital with oral ciprofloxacain, adequate analgesic, ondansetron and nadroparin prophylaxis. Urine culture was collected.

Macroscopic hematuria with clots continued intermittently at the second day of admission and lab parameters showed an increased CRP to 130 mg/L, worsening of the eGFR to 42 ml/min/1.73m^2 and doubling of serum creatinine to 125 µmol/L (Table 1). Therefore, a nephrostomy catheter was introduced and hydration was increased.

Although the renal parameters gradually improved, the patient developed spiking fever. Antibiotic treatment was switched to intravenous cefuroxime with a one-off dose of tobramycin. A thoracic X-ray ruled out a hospital acquired pneumonia and showed minimal basal atelectasis without any other aberrations. Urine culture showed E. coli growth, sensitive to ciprofloxacain and cefuroxime among others.

The spiking fever persisted and the patient developed slight anemia (hemoglobin 6.4 mmol/L). A second abdominal CT at day three showed signs of extending pyelonephritis and resorption of the ureteral blood clot, but no indication for abscesses (Fig. 2). Antibiotic treatment was switched to intravenous ceftriaxone, without subsequent improvement of fever or relief of symptoms. Nevertheless, the renal parameters remained gradually improving and urine production was stable and sufficient.

Furthermore, the patient noted a decrease in vision of the right eye at day four. Fundoscopy showed diffuse retinal capillary micro-bleeding in the right eye, characteristic for a thrombotic venous occlusion
(Fig. 3). Beta-blocker eye droplets were prescribed. The prophylactic dosage of nadroparin was not increased to a therapeutic dosage after consulting the vascular specialists. Follow up through fundoscopy every other day showed no further changes during the admission.

At day six, a third abdominal CT was performed and was compatible with an ongoing pyelonephritis. There were multiple hypodense areas. As a renal abscess could not be ruled out, an attempt for drainage of the suspected presumed abnormality was performed. However, the drainage revealed solely swollen hydrous kidney parenchyma without purulence.

As fever-spikes up to 40.4 degrees Celsius lingered through admission, another real-time reverse transcription PCR for SARS-COV-2 from a throat swab sample was performed at day seven, with a negative result.

Due to diarrhea with mucus admixture, PCRs of campylobacter coli/jejuni, salmonella, shigella and yersinia enterocolitica were performed, all with a negative result. The diarrhea ceased spontaneously within five days.

Sudden and recurrent symmetrical paresthesia and severe lower back pain during consecutive nights were indications to perform a cerebral and spinal MRI at day eight, which did not show any abnormalities. In addition, also in respect to the ocular vascular occlusion, a carotid and vertebral artery duplex analysis was performed at day eight, without any aberrations.

Although antibiotic treatment for sepsis was adequate, the clinical condition of the patient did not improve thus far. An urgent multidisciplinary meeting with the departments of urology, infectious disease, microbiology, neurology, and ophthalmology did not result in an added diagnosis or full explanation of the woman's symptoms. Analysis for the persistent fever was continued by extensive determination of systemic and (auto-)immunogenic disorders (Table 2), but no indications were found. The International Normalized Ratio (1.1) and the activated partial thromboplastin time (25, range 24–33 seconds) were not aberrant. The anemia remained stable throughout admission, with a minimum hemoglobin level of 6.0 mmol/L. All blood, urine and drainage fluid culture analyses resulted in growth of E.coli with sensitivity for ciprofloxacin, cefuroxime and ceftriaxone.
Table 2
Systemic and (auto)immunogenic parameters

| Test                               | Reference range | Result |
|------------------------------------|-----------------|--------|
| IgG4, g/l                          | 0.08–1.4        | 0.34   |
| ANCA anti-PR3                      | 0.0–3.0         | 0.3    |
| ANCA anti-MPO                      | 0.0–5.0         | 0.2    |
| ANA                                | 0.0–1.5         | < 0.5  |
| Anti-dsDNA, U/ml                   | 0.0–15.0        | 0.7    |
| Cardiolipin IgM, U/ml              | 0–40            | 9.4    |
| Cardiolipin IgG, U/ml              | 0–40            | 30.0   |
| Beta-2-glycoprotein I IgM, U/ml    | 0–10            | < 0.01 |
| Beta-2-glycoprotein I IgG, U/ml    | 0–10            | 1.3    |
| lupus anticoagulant                |                 | undetectable |
| CH-50, %                           | 68–133          | 122    |
| C1q (subfactor C1), IE/ml          | 81–128          | 129    |
| C3 (determined with anti-C3c), g/L | 0.9–1.8         | 1.54   |
| C4, mg/L                           | 150–400         | 180    |
| DAT IgG                            | neg             | neg    |
| DAT C3b/3d                         | neg             | neg    |
| DAT Titer                          |                 | 1:1    |
| JAN2 V617F mutation                |                 | undetectable |

The symptoms of fever and flank pain slowly decreased at the 10th day of admission and the catheter was removed. The fever disappeared two days later. The patient further recuperated till acceptable condition to discharge at day 17 with oral ciprofloxacin treatment for another 10 days.

**Follow-up**

The patient returned to the ER one week later due to complains of the nephrostomy and was advised to hydrate and continue analgesics. There were no indications for a (recurrent) infection.

Three weeks after discharge, an antegrade pyelography revealed effective and easy passage of fluid to the bladder. Two months later, a micturating cystourethrogram (MCUG) did not show any signs of urinary reflux or anatomical deviations. Thereafter, the nephrostomy was successfully removed.
At four months after discharge, a CT-scan for follow-up showed clear decrease of volume of the right kidney compared to the CT at admission (Fig. 4). At the site of the preceded pyelonephritis, an irregular aspect of the surface of the interpolar region and inferior pole and decreased density suggested scarring of the renal cortex. The previous multiple small concrements were observed as unchanged. By multidisciplinary consultation, a one-year follow-up was chosen for monitoring blood pressure, serum creatinine/eGFR and urinal protein level.

Follow-up of the eye through repetitive fundoscopy showed gradual improvement of the quantity and sizes of the retinal bleeding sites. However, remnant bleedings in the peripheral retina were still visible at three months after discharge.

**Discussion**

In this report, we describe an unusual course of disease of a young female with atypical pyelonephritis, persistent fever, and multiple blood clotting and hemorrhagic events one week after recovery from COVID-19. To our knowledge, this is the first description of the association of pyelonephritis with COVID-19.

The exact origin of the ureteral blood clot remains unknown. The pyelonephritis may have caused hemorrhage/hematuria due to infection and may cause consecutive formation of the obstructive blood clot in the upper urinary tract. However, the contrary causative course of an ureteral blood clot that led to pyelonephritis cannot be ruled out. Hemorrhagic pyelonephritis is extremely rare and its prevalence is unknown. Spontaneous renal hemorrhage is caused by infection in only 2% of cases [6]. However, hemorrhagic cystitis can be initiated by both bacteria and viruses [7]. Thus, the presumed course of events in this patient is a hemorrhagic event or infection of the urothelium, causing an obstructive blood clot in the ureter and consecutive urinary stasis and hydronephrosis. The ensuing bacterial infiltration of the renal parenchyma grounds initiating or worsening of the pyelonephritis. Subsequent development of fever due to the bacterial invasion of the renal tissue and acute decreased kidney function are in line with the course of disease. The urinary and serum culture indeed showed excessive growth of E. coli, known to be regularly present in urine and causative for 80% of pyelonephritis cases [4].

Direct SARS-COV-2 or indirect systemic inflammation related tissue damage of the kidney and urothelium is suggested to be linked to the observed hemorrhage in the urinary tract. Interestingly, proximal tubule cells of the kidney and bladder urothelial cells highly express the receptor angiotensin converting enzyme II (ACE2); the receptor utilized by the SARS-CoV-2 virus to enter human cells [8]. The kidney and urinary tract are hence considered highly at risk of direct viral injury. In addition, as in other coronaviruses, pathology from autopsies and laboratory analysis of COVID-19 patients show there is a high renal involvement with acute tubular necrosis (ATN) within 3 weeks after onset of symptoms as the most common cause [9, 10]. Likewise, the described patient presented to the ER with flank pain and hematuria exactly 3 weeks after the onset of COVID-19 symptoms. Indeed, 26.7% of patients with COVID-19 present with hematuria at time of admission, and 44% eventually develop hematuria and proteinuria during admission [3]. Suspect etiologies for ATN include renal hypoperfusion, cytokine release syndrome, organ
crosstalk, systemic effects and, as discussed, direct viral invasion [5]. Thus, although a direct link between pyelonephritis and COVID-19 is not yet established, a preceding renal-injury-based hemorrhage is suspected to have provoked above-described course of events towards bacterial pyelonephritis.

The repeated culture of the E.coli showed sufficient sensitivity to all prescribed oral and intravenous antibiotics, while there was a delayed (clinical) response to the antibiotic treatment. The most probable factor is the swollen spongy aspect of the renal parenchyma. Intermittent (spiking) fever is typical for the presence of an abscess, which was, howbeit, ruled out by CT in combination with an image-guided puncture [11]. Still, the swollen parenchyma is a “fluid reservoir”, which might be comparable in regard to subsequent intermittent fever and decreased drug penetration [12]. Furthermore, inflammation may have caused decreased perfusion of the infected tissue. Ronco, et al. suggested COVID-19 related renal tissue injury based on excessive cytokine release and intrarenal inflammation [5]. Such cytokine release syndrome may lead to systemic hypotension and renal hypoperfusion, decreasing the glomerular filtration rate. In addition, an excessively high concentration of anti-inflammatory mediators may predispose the COVID-19 patient to a state of relative immunosuppression [5]. Not only may such mechanisms worsen the clinical course of the bacterial pyelonephritis, it may also decrease the effectiveness of the antibiotic treatment.

There was a clear discrepancy between the clinical presentation of the patient, lacking systemic symptoms, and the morphology of the diseased kidney on CT. Although fever may be absent in an early stage, the simultaneous spongy aspect of the enlarged renal parenchyma was unusual in this case of pyelonephritis [13, 14]. The aspect of the kidney on CT was comparable to cases of Xanthogranulomatous pyelonephritis (XPN) [14], corresponding to dilated calyces lined with necrotic xanthomatous tissue extending into the renal parenchyma. This unusual variant of chronic pyelonephritis may, in this patient, have occurred due to the ureteral blood clot as the obstructive moment. With a medical history of previous pyelonephritis and as XPN indicates a chronic process based on recurrent infections, a XPN-like form of pyelonephritis is considered.

The follow up, with two previous events of pyelonephritis in mind, was mainly focused on ruling out any anatomical, mechanical or functional underlying pathophysiology. The antegrade pyelography showed effective passage of contrast and the MCUG did not show any signs of urinary reflux or anatomical deviations. The CT at 4 months after discharge showed decreased right kidney volume and potential diffuse renal tissue scarring, without signs of other abnormalities. Therefore, there are no radiological indications for vesicoureteral reflux or any other physical explanatory mechanisms for the persistent fever and recurrent pyelonephritis.

In a far greater number than hemorrhagic events, hypercoagulation has been a well described complication in COVID-19 [1]. The thrombotic venous occlusion in the right eye increases the suspicion of coagulopathy in this patient. However, no abnormalities in hemostatic parameters were found during admission and the vascular sonography of the head and neck was normal. Nevertheless, a causal relationship with the preceding COVID-19 remains plausible. Thrombotic complications, including ocular
vascular occlusion, has been described while being on therapeutic anticoagulation in up to 31% of COVID-19 patients [2, 15]. Although a similar event was diagnosed in our patient, no proven active SARS-CoV-2 infection was established at the moment of the event. Interestingly, other case reports also described the end of COVID-19 symptoms 10–14 days prior to a retinal vein occlusion [16, 17]. In addition, a case report of a COVID-19 related renal infarct by Wu, et al. suggests a hypercoagulative state that may persist long after the resolution of COVID-19 [18].

It is remarkable that the patient presented with several unexplained symptoms during admission. The diarrhea with mucus admixture followed an unusual course to explain by antibiotic or other drug treatment, as it developed in a conflicting timeframe. Moreover, the sudden and recurrent paresthesia and lower back pain could not be linked to any pathophysiological process.

In conclusion, we present the case of a 35-year-old woman, five days after having recovered from a SARS-CoV-2 infection, with an unusual course of bacterial pyelonephritis based on an obstructive ureteral blood clot in combination with persistent fever and an ocular thrombus. We hypothesize that COVID-19-related cytokine effects, renal inflammation and systemic effects deteriorated the clinical course of the pyelonephritis and possibly even the occurrence of an ureteral hemorrhage. COVID-19-related coagulopathy is suspected to have caused the venous retinal occlusion. The swollen renal parenchyma is suggested causative for the persistent fever despite adequate intravenous antibiotic treatment. However, the fulminant course of disease parallel to multiple unexplained symptoms remain aspects of this case that are yet to be fully understood. This case report emphasizes the need for further research on the unexplored relationship between pyelonephritis and COVID-19. Awareness to delayed hemorrhagic and hypercoagulative events in post-COVID-19 patients is required.

Declarations

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All the authors have declared no funding was received for writing and publication of this case report

Conflicts of interest

All the authors have declared no competing interests.

Ethics approval

Informed consent of the patient was obtained for writing and publication this case report.

Consent to participate

Informed consent of the patient was obtained for writing and publication this case report.

Consent for publication
Informed consent of the patient was obtained for writing and publication this case report.

**Availability of data and material**

All the authors declare data and (visual) material in this case report has not been re-used, copied, summarized or paraphrased and has not been published before in any sort.

**Code availability**

n.a.

**Authors’ contributions**

L.J. van ’t Hof: data acquisition, literature research, writing of the manuscript.

L. Pellikaan: editing the manuscript.

D. Soonawala: consulting nephrologist; editing the manuscript.

H. Roshani: consulting urologist; editing the manuscript, supervision of the literature study.

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