

Case Series of the Month

Urinary Frequency as a Possibly Overlooked Symptom in COVID-19 Patients: Does SARS-CoV-2 Cause Viral Cystitis?

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Abstract

The current coronavirus disease 2019 (COVID-19) pandemic is a challenge for physicians in triaging patients in emergency rooms. We found a potentially dangerous overlap of classical urinary symptoms and the as yet not fully described symptoms of COVID-19. After a patient was primarily triaged as a urosepsis case and then subsequently diagnosed with COVID-19, we focused on an increase in urinary frequency as a symptom of COVID-19 and identified this in seven males out of 57 patients currently being treated in our COVID-19 wards. In the absence of any other causes, urinary frequency may be secondary to viral cystitis due to underlying COVID-19 disease. We propose consideration of urinary frequency as an anamnestic tool in patients with infective symptoms to increase awareness among urologists during the current COVID-19 pandemic to prevent fatal implications of misinterpreting urological symptoms.

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1. Case series

1.1. Background

After its initial discovery in Wuhan, China the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread throughout the world and the consecutive coronavirus disease 2019 (COVID-19) was declared a pandemic by the World Health Organization shortly afterwards [1]. As

the pandemic is still in an early phase and many symptoms have not yet been fully described [2], careful clinical observation is of paramount importance. Rocco et al [3] pointed out the importance of early recognition of symptoms by urologists for proper triage of patients and to prevent missing possible SARS-CoV-2 infection because of an overlap of COVID-19 and classical urological symptoms. We believe that in addition to fever, an increase in urinary frequency should be considered as an important

overlapping symptom with urosepsis in the differential diagnosis of COVID-19 both in ambulatory care and in emergency rooms.

1.2. Cases

A case with suspected urinary sepsis was admitted to the emergency department of a university hospital. The patient reported fever, shivering, flank pain, urgency, and increased urinary frequency as initial symptoms. Initial urine analysis via urine sediment and urine culture demonstrated no signs of infection. The patient was discharged home with oral antibiotics. As part of the routine work-up in German hospitals, a nasopharyngeal swab that had been taken on the same day revealed a positive result for SARS-CoV-2 by polymerase chain reaction (PCR) the following day. Subsequently, the patient was admitted to one of our specialized COVID-19 wards with aggravating symptoms including fever, fatigue, and breath-dependent chest pain.

Urinary frequency is a common symptom in urinary infection. In order to investigate if this was present in other patients with COVID-19, we retrospectively and prospectively looked at patient histories for the presence of urinary frequency on admission to our specialized COVID-19 wards. In the time period from March 16 to April 13, 2020, seven males out of 57 patients reported an increase in urinary frequency along with dry cough ($n=5$), fever ($n=3$), and shortness of breath ($n=3$) as leading symptoms (Tables 1 and 2). All patients tested positive for SARS-CoV-2 in nasopharyngeal swabs and developed pulmonary symptoms detectable on imaging (Fig. 1). Micturition protocol revealed an average of 13.7 micturitions per day on the day of admission and 11.6 on day 5. In all patients, urinary infection, acute renal injury, and prostatitis were excluded by urine analysis and normal serum creatinine and prostate-specific antigen (PSA), respectively. Prostate volumes were evaluated via ultrasound, which revealed mildly enlarged prostates in all patients; there were no signs of residual urine or significant bladder wall thickening. SARS-CoV-2 RNA was not detected by PCR in any urinary specimens taken from all the patients during the first week after admission. Two patients had detectable SARS-CoV-2 RNA in serum during this period (Ct value 40; Tables 3 and 4). None of the patients required admission to the intensive care unit. The average length of stay was 15 d.

2. Discussion

The reason for higher urinary frequency is unclear so far, as the patients had no signs of acute kidney injury, bacterial infection, or prostatitis. We suspect that viral cystitis due to SARS-CoV-2 causes the urinary frequency symptom. It is unclear whether replication of SARS-CoV-2 RNA in urothelial cells or secondary effects due to local or systemic inflammation, such as endotheliitis [4], are a hallmark in COVID-19 patients leading to symptoms such as irritative symptoms of the lower urinary tract and high urinary frequency. Interestingly, three patients presented with microhematuria, which possibly further supports the

Table 1 – Patient characteristics.

Parameter	Result
Median age, yr (range)	62 (59–78)
Median MuLBSTA score (range) ^a	9 (6–15)
Male, n (%)	7 (100)
Chronic underlying condition, n (%)	
Hypertension	5 (71.4)
Cardiac disease	2 (28.6)
Obesity	2 (28.6)
Diabetes	2 (28.6)
Cancer	2 (28.6)
Renal disease	1 (14.3)
Benign prostatic hyperplasia	1 (14.3)

^a The MuLBSTA score is used to predict 90-d mortality in viral pneumonia [10].

Table 2 – Symptoms on admission.

Symptom	Patients, n (%)
Increased urinary frequency	7 (100)
Dry cough	5 (71.4)
Fever	3 (42.9)
Shortness of breath	3 (42.9)
Diarrhea	1 (14.3)
Shivering	1 (14.3)

hypothesis of SARS-CoV-2-induced viral cystitis on infection of urothelial cells. Conversely, we did not detect viral RNA in the urine of these patients, so it seems that urine is unlikely to be a potential source of infection, at least in our cohort.

2.1. Potential mode of action

Recent studies revealed the cell-surface protein angiotensin-converting enzyme 2 (ACE2) as the main receptor for the SARS-CoV-2 spike protein [5]. Investigations of the distribution across many different tissues revealed that ACE2 expression was highest in lung, intestines, and kidney, but it was also high in 2.4% of urothelial cells, potentially increasing their susceptibility to infection with SARS-CoV-2 and possible subsequent viral cystitis [6]. As viral RNA has been detected in urine of COVID-19 patients [7], it can be hypothesized that infection of tissues of the urinary tract might cause an increase in urinary frequency. Detection of SARS-CoV-2 RNA in serum of two hospitalized patients, similar to detection of elevated IL-6 [8], is suggestive of the assumption that urinary frequency occurs as a complication in these patients in the course of a more severe stage of infection. Despite the presence of ACE2 in the urogenital tract, negative urinary PCR results do not support the assumption of strong or even relevant continuous replication in (luminal) tissues of the efferent urinary tract. Since it is unclear whether the receptor is expressed in luminal or basal urothelial cells, the route by which SARS-CoV-2 might cause viral cystitis could be via either viremia from the basal side or urine from the luminal side of urothelial tissue. The

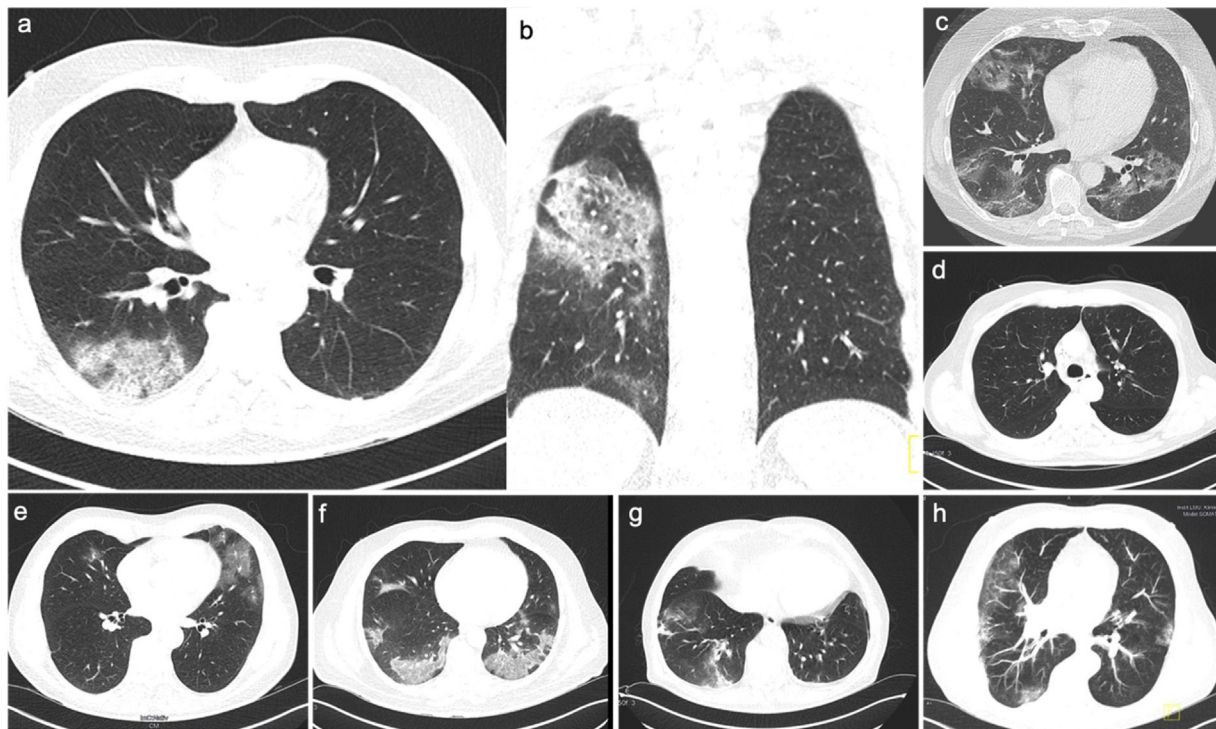


Fig. 1 – Lung imaging for all the patients. Computed tomography lung imaging was performed for all patients on admission (± 5 d). All patients showed signs of viral pneumonia, as evidenced from the images. (A,B) Images for patient 1 in the coronal and axial planes. (C–H) Images for patients 2–7, respectively, in the coronal plane. Predominantly bilateral ground glass opacification and typical COVID19-associated crazy paving areas are evident (C,F,H).

COVID19 = coronavirus disease 2019.

absence of viral RNA in urine and the detection of SARS-CoV-2 in serum of two patients might indicate a role of infection in basal urothelial cells via blood that then causes cystitis. In addition, it has been postulated that endotheliitis

might play a role in COVID-19 patients [4] and might contribute to local inflammation in the bladder (Fig. 2). Further evidence is urgently needed for a fuller understanding of the possible molecular mechanisms.

2.2. Clinical implications

Classical symptoms of urinary tract infection or urosepsis such as fever and frequent urination might be misleading during the current COVID-19 pandemic. In general, diagnosis of COVID-19 is challenging as patients often present with unclear or even subclinical signs of disease [9]. Contaminated

Table 3 – Pulmonary imaging and virological and laboratory results.

Test	Result
Atypical pneumonia on computed tomography, n (%)	7/7 (100)
SARS-CoV-2 RNA nasopharyngeal swab, n (%) ^a	7/7 (100)
SARS-CoV-2 RNA in serum, n (%) ^a	0/3 (0)
SARS-CoV-2 RNA in serum, n (%) ^b	2/4 (50)
SARS-CoV-2 RNA in urine, n (%)	0/6 (0)
Mean prostate volume, ml (range)	53 (35–66)
Mean residual urine, ml (range)	14.3 (0–40)
Mean urine osmolality, mosm/kg (range) ^a	547.6 (383–702)
Mean prostate-specific antigen, ng/mL (range) ^a	1.47 (0.3–3.6)
Mean creatinine, mg/dl (range) ^a	0.92 (0.7–1.4)
Mean creatinine, mg/dl (range) ^b	0.87 (0.6–1.6)
Mean maximum IL-6, pg/mL (range)	215 (26.3–1086)
Mean procalcitonin, ng/mL (range) ^a	0.1 (>0.1–0.4)
Mean lactate dehydrogenase, U/l (range) ^a	334 (223–565)
Mean leukocytes, g/l (range) ^a	5.9 (2.8–9.7)
Mean neutrophils, % (range) ^a	64 (41–92)
Mean lymphocytes, % (range) ^a	18 (6–30)
Mean eosinophils, % (range) ^a	0.7 (<1–2)

^a Day 0–5.

^b Day 5–10.

Table 4 – Standard urinary analysis.

	Patients, n (%)
Urinary infection	0/7 (0)
Urine dipstick	
Negative for leukocytes	7/7 (100)
Urine sediment	
Negative for leukocytes	2/4 (50)
1–3 leukocytes per high-power field	2/4 (50)
Microhematuria	3/4 (75)
Urine cultures negative ^a	6/6 (100)

^a Urine culture was not performed for one patient for whom the urine dipstick and urine sediment were negative for leukocytes.

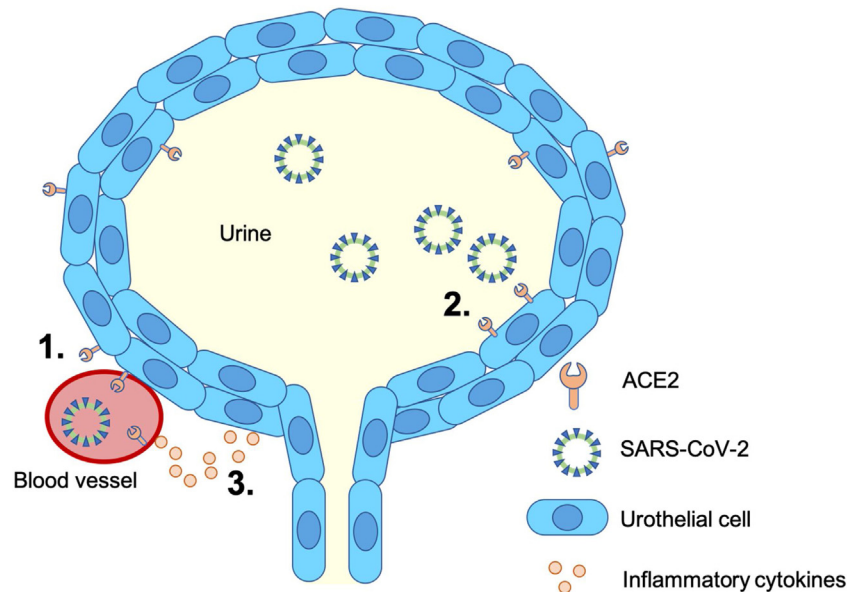


Fig. 2 – Potential mode of action. ACE2 has been described as the receptor for SARS-CoV-2, so urothelial cells might be affected in COVID-19 patients [6]. As localization of expression is unclear so far, basal or luminal expression is possible, so two possible infection routes could be hypothesized: (1) infection via capillaries is possible, especially in the light of viraemia an infection route of interest; (2) infection via urine might be possible, as SARS-CoV-2 has been detected in urine elsewhere [7]. (3) Alternatively, cystitis might be secondary due to local inflammation (eg, endotheliitis) [4]. ACE2 = angiotensin-converting enzyme 2; COVID19 = coronavirus disease 2019; SARS-CoV-2; severe acute respiratory syndrome coronavirus 2.

urine samples may hamper accurate interpretation of urine diagnostics. Furthermore, urological patients often have ureteral stents or other prosthetic materials that can lead to infected sediments in urine analysis. As these patients are often elderly or immunocompromised with comorbidities such as cancer or diabetes, they represent a high-risk cohort for both urosepsis and severe COVID-19 disease. We therefore believe that in the current COVID-19 pandemic, laboratory work-up should include blood tests such as full blood count, interleukin-6, ferritin, procalcitonin, PSA (in males), and C-reactive protein, as well as urinary examination (microscopy and culture) and nasopharyngeal swab testing for SARS-CoV-2 RNA. These diagnostic tools may be critical for differentiation between COVID-19 and urological diagnoses in patients presenting with urinary frequency.

2.3. Conclusions

We identified higher urinary frequency as an additional symptom of SARS-CoV-2 infection independent of acute renal injury or urinary tract infection in a small series of hospitalized patients. Since urinary frequency along with clinical signs such as fever and positive laboratory results for inflammatory markers may be misinterpreted as urosepsis, knowledge of this finding is important for urologists during the current COVID-19 pandemic. Further research is warranted to understand the molecular mechanisms leading to urinary frequency, potentially attributed to viral cystitis in SARS-CoV-2-infected patients, and to determine its prognostic value.

Conflicts of interest: The authors have nothing to disclose.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.eururo.2020.05.013>.

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