Crystals in Urine Microscopy in A COVID-19 Patient: Case Report

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Abstract
Due to novelty of Coronavirus disease, the understanding of its pathology, clinical outcomes, prognostic factors, and treatment is still in its nascent stage. Kidney dysfunction is reported in many patients. We report a finding of an uncommon form of urine crystals in a RT-PCR confirmed case of COVID-19 patient. RT-PCR confirmed case of COVID-19 patient, no clinical history of renal calculi reported until day 7 of the treatment. Treatment mainly comprised of favipiravir, vitamin C and zinc. On seventh day of treatment the patient became asymptomatic but the crystals were observed in the urine. The loading dose of favipiravir in COVID-19 positive patient considered as the reason for the urine crystals. In view of nephrotoxic nature of the disease as well as the drugs used in its therapy, it is important to look for subtle signs as well as inexpensive tests which can give vital information, to pick these complications early. Although this observation was made on a single patient, contributions from multiple centres can help understand this further, with keen observation on urine microscopy of COVID-19 patients.

Keywords: Crystals; Favipiravir; COVID-19; Urine microscopy; Urinary crystals

Introduction
Coronavirus Disease (COVID-19) is a relatively new disease to all of us and we are still in the process of understanding its pathology, clinical outcomes, prognostic factors, and treatment. Kidney dysfunction is not uncommon in COVID-19 patients, with about one third of hospitalized patients showing acute kidney injury (AKI). Acute kidney injury has also been linked with poorer prognosis, in COVID-19 patients[1]. Favipiravir is metabolized to an inactive metabolite M1 by aldehyde oxidase and xanthine oxidase, and excreted into urine. Favipiravir and M1 act as moderate inhibitors of organic anion transporter 1 and 3 (OAT1 and OAT3), which are involved in uric acid excretion in the kidney. In addition, M1 enhances uric acid reuptake via urate transporter 1 (URAT1) in the renal proximal tubules. Thus, favipiravir is thought to decrease uric acid excretion into urine, resulting in elevation of uric acid levels in blood. Increase in blood uric acid is a frequently seen side effect of favipiravir therapy[2]. Favipiravir has also been demonstrated as nephrotoxic in COVID-19 patients[3]. Half life of Favipiravir is observed to reach highest concentration in blood (Cmax) within two hours of ingestion, with a half-life of 2.5 to 5 hours, due to rapid renal elimination[4]. Excessive Vitamin C administration has also been considered a likely cause of acute tubular injury (ATI) and oxalate nephropathy[1]. Vitamin C, when given intravenously at high doses, may also cause urinary
crystals, which are made up of calcium oxalate indistinguishable from calcium oxalate crystals from other causes\textsuperscript{[5]}. However, we couldn’t find any articles mentioning the presence of crystals in the urine of COVID-19 patients. In this regard, we report a finding of an uncommon form of urine crystals in a RT-PCR confirmed case of COVID-19 patient.

**Case presentation**

A 24-year-old male presented with non-productive cough. He tested positive for SARS-CoV-2 on the following day (Day 2 of symptoms), after which he was started on following treatment: (i) tablet Favipiravir 1800 mg BD as loading dose followed by 800 mg BD for another 6 days, (ii) tablet ivermectin 12mg OD (3 alternate days), (iii) tablet doxycycline 100mg BD, (iv) tablet zincovit BD, (v) tablet limcee TDS, capsule.aquasol BD, (vii) cholecalciferol 60,000 IU (once a week for 4 weeks).

Two hours after taking the above-mentioned drugs, he gave his sample for Urine routine and microscopy along with other blood investigations (namely CBC, CRP, D-dimer, Liver Function Test, Uric acid, Urea, Creatinine, Electrolytes).

All blood parameters mentioned above were within normal limits, except slightly high bicarbonate and chloride in electrolytes. Urine was acidic in pH, and proteins, sugar, ketone, bile salt and bile pigments were absent. Light microscopy of centrifuged wet mount of urine showed presence of 0 - 2 of pus cells, RBCs and epithelial cells on each high-power field (HPF). The most striking finding was presence of numerous needles shaped, colourless to pale yellow crystals, seen singly as well as in bundles like a broom (See picture below). The following differentials were considered for the crystals: Sodium urate crystals, Sulphonamide/Sulphadiazine crystals, Tyrosine crystals, Indinavir crystals.

Further history of the patient revealed he had no personal or family history of metabolic disorders or any history of long-term drug ingestion in the past. Thus, tyrosine and indinavir crystals were ruled out.

Follow-up urine routine on day 5 and day 7 of illness did not show these crystals. Favipiravir therapy ended on day 6. Clinically, the patient was asymptomatic, besides the cough mentioned above which lasted until this report was written (7 days of illness). The patient had no history of crystals in urine in any past reports, nor any clinical history of renal calculi.

**Discussion**

Nephrotoxicity has been seen as a complication of COVID-19 as well as the drugs used in its treatment. Early detection of renal involvement may help to reduce mortality and morbidity in patients with COVID-19 infection\textsuperscript{[6]}. Thus, attempts should be made to understand and pick up early signs of this insult.

A simple inexpensive microscopic examination of the urine early in the disease may give us clues to understand which patient may or may not develop renal issues.
Absence of articles on crystals in urine microscopy of COVID-19 patients limited our understanding on this topic, however, it is interesting to note that the time of urine collection matched with the Cmax of Favipiravir. Thus, we suspect the loading dose of Favipiravir as the reason for these urine crystals. Certain aspects need to be focused: incidence of these crystals in general population as against in COVID-19 patients, are these crystals caused by the high loading dose of Favipiravir (since these crystals weren’t seen in subsequent samples), and clinical significance of these crystals.

Hopefully, we shall have a clearer understanding about this as we study more and more patients, but for this to happen, the basic test of urine routine and microscopy should be asked in all COVID-19 patients, especially at the time of initiating therapy. Another aspect of understanding this phenomenon would be taking multiple samples in a day.

**Conclusion**

In view of nephrotoxic nature of the disease as well as the drugs used in its therapy, it is important to look for subtle signs as well as inexpensive tests which can give vital information, to pick these complications early. Although this observation made on a single patient, contributions from multiple centres can help understand this further, with keen observation on urine microscopy of COVID-19 patients.

**Disclaimer**

The authors are well aware that this observation may be completely unrelated to COVID-19 in the patient mentioned above. However, as our understanding of COVID-19 is evolving, it is important to put all the information out there to draw well rounded conclusions.

**Patient consent:** N/A

**Conflict of Interest:** Nil

**Financial Disclosure:** None

**References**