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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Table S1. Sensitivity analysis in participants with suppressed HIV-RNA, excluding participants on unboosted PIs ($n = 100^*$).

Table S2. Sensitivity analysis excluding participants on raltegravir ($n = 177^*$).

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1-Methyluric Acid Nephropathy



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Crystalline nephropathies may be responsible for acute kidney injury and are probably underdiagnosed. Many drugs may induce acute kidney injury due to intratubular precipitation, especially antiretroviral drugs and antibiotics including

amoxicillin, sulfadiazine, sulfamethoxazole, and, as recently reported, vancomycin.^{1–3} Metabolic end-products can crystallize in the renal tubule, mainly calcium oxalate monohydrate in patients affected by primary or enteric hyperoxaluria or after ethylene glycol

poisoning.⁴ Purine metabolites also may precipitate in the renal tubule and promote acute kidney injury: uric acid in Lesch-Nyhan syndrome, uric acid or xanthine after lysis syndrome, and 2-8 dihydroxyadenine in patients affected by adenine phosphoribosyl transferase mutation.^{1,5,6}

The main caffeine metabolite identified in urine is 1-methyluric acid.⁷ Some rare kidney stones made of 1-methyluric acid have been reported previously. One patient with a past medical history of rheumatoid arthritis and gouty attacks, and with a nephropathy attributed to analgesic abuse, was affected by kidney stones made of 1-methyluric acid.⁸ He was an avid coffee consumer (8 cups/d). During the past 40 years, 20 stones made at least partly of 1-methyluric acid have been analyzed in the Necker and Tenon hospital laboratory.⁹ Most of these patients underwent hemodialysis and all received aluminum hydroxide, suggesting that this compound could interfere with caffeine metabolism.

To date, 1-methyluric acid nephropathy has not been reported and we discuss herein 3 biopsy-proven cases.

RESULTS

Clinical and Biological Data

Case 1

A 64-year-old woman received a kidney allograft in 2018, after 5 years on hemodialysis, in Necker Hospital, Paris, France. End-stage renal disease was due to chronic lithium therapy and she had micropolycystic bilateral native kidneys. She did not receive aluminum salts while on hemodialysis. On admission, she was on aripiprazole for a stable bipolar disease, and received esomeprazole and classic immunosuppressive drugs: prednisone, mycophenolate mofetil, and tacrolimus. The pre-implantation allograft biopsy did not show any specific lesion. On the first month following the kidney allograft, she developed a severe nonobstructive acute kidney injury (serum creatinine level: 645 $\mu\text{mol/l}$, vs. nadir serum creatinine level at 160 $\mu\text{mol/l}$ a few days after the graft), tubular proteinuria (0.8 g/g creatinine), and mild aseptic leukocyturia (white blood cell count: 12/ mm^3). She did not report abdominal pain. Crystalluria was positive with round-shaped crystals (urine pH: 6.8) and polarized light microscopy of the urine sediment revealed a central maltese-cross pattern within crystals (Figure 1a). Granular casts and phagocytosis of crystals in urine were found, evocative of intrarenal inflammation (Figure 1b). A kidney biopsy was performed.

Case 2

A 36-year-old man was referred in 2019 to an emergency unit for fatigue and altered general state in Douai Hospital, France. He was a drug addict (heroin) and on

buprenorphine for drug substitution. Acute renal failure was diagnosed (serum creatinine level 410 $\mu\text{mol/l}$) with heavy hematuria (380/ mm^3) and leukocyturia (136/ mm^3) associated with mild tubular proteinuria (0.9/g creatinine). Obstructive acute kidney injury was ruled out by abdominal echography. A kidney biopsy was performed. He did not report abdominal pain.

Case 3

A kidney biopsy from a 33-year-old male drug addict with acute kidney injury was sent to Necker Hospital laboratory in 1999 and analyzed retrospectively. No biological or clinical data were available.

Histopathology

Percutaneous kidney biopsies were performed in the 3 cases and histopathological data were collected for cases 1 and 2. Paraffin sections were stained with hematoxylin-eosin and Masson trichrome, and analyzed on light microscopy, with polarization. Biopsies presented patterns of diffuse acute tubular necrosis. Important inflammatory infiltrate was present in case 1 but absent in case 2. Intratubular material was present in case 2 with greenish periodic acid–Schiff–positive structures (Figure 1c). No sign of rejection was identified in case 1 but severe vascular lesions were present in the kidney allograft.

Under polarized light, polarizing intratubular deposits were identified in cases 1, 2, and 3 (Figure 1d). Immunofluorescence was negative for immunoglobulins and complement subunits. In case 2, immunohistochemistry was performed with anti-MUC1 antibody and identified that crystals predominated in the distal tubule (Figure 1e).

Case 1 biopsy was studied by scanning electron microscopy, revealing the presence of massive tubular plugs (Figure 1f).

Infrared Spectroscopic Analyses

Fourier-transform infrared spectroscopic analyses were performed on frozen kidney biopsy sections on specific low-emission slides (cases 1 to 3). In the 3 cases, the polarizing deposits were made of 1-methyluric acid crystallites, with distinctive vibrations, for instance at 1027 cm^{-1} , 1753 cm^{-1} , 852 cm^{-1} , and 3 peaks between 700 and 800 cm^{-1} (typical in purines) in reflectance Fourier-transform infrared spectroscopic analysis (Figure 1g). Fourier-transform infrared spectroscopic analysis was also performed on the crystals collected from case 1 urine, confirming they were made of 1-methyluric acid. Reference spectra were obtained from previously analyzed stones made of 1-methyl uric acid and uric acid (Figure 1h and i).

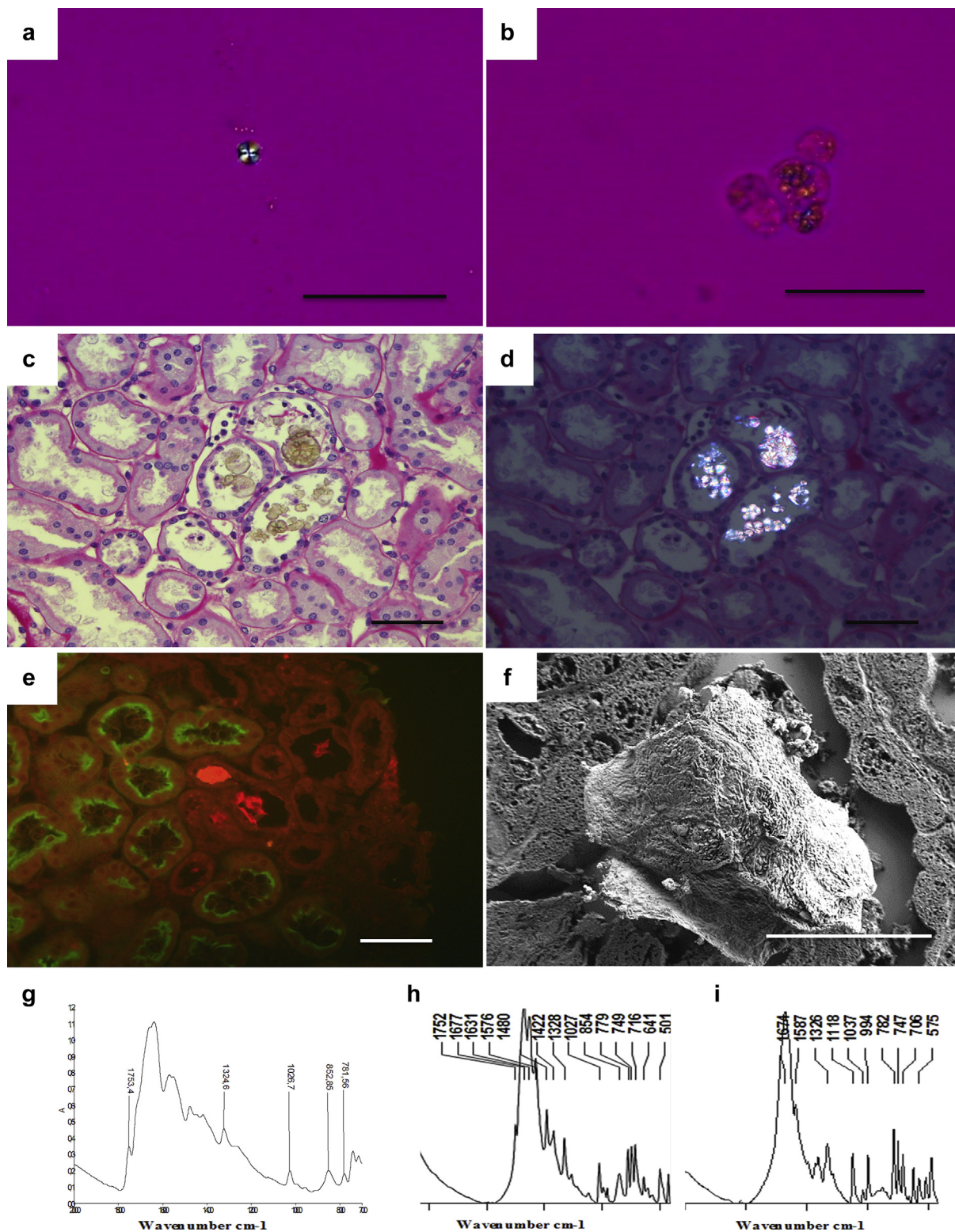


Figure 1. Crystals of 1-methyluric acid in urine and kidney biopsies. (a) Crystalluria, 1-methyluric acid crystals in urine (case 1) were round-shaped with a central *maltese cross*. Bar = 25 μm . (b) Crystals of 1-methyluric acid were sometimes inside macrophagic cells in urine. Bar = 25 μm . (c,d) Periodic acid-Schiff staining. Intratubular crystallites (case 2) were brown/greenish and refractive in polarized light. Bar = 25 μm . (e) MUC1 immunostaining (red) revealed that crystals were mostly observed within distal tubules and not in the proximal tubules stained in green by lectin *Lotus Tetragonolobus*. Bar = 25 μm . (f) Scanning electron microscopy evidenced massive and poorly organized crystallites in renal tubules. Bar = 25 μm . (g) Fourier-transform infrared reflectance spectrum evidencing the presence of 1-methyl uric acid in kidney biopsies. (h) Transmittance Fourier-transform infrared spectroscopic analysis reference spectrum obtained from a 1-methyl uric acid stone. (i) Uric acid (dihydrate) transmittance Fourier-transform infrared spectroscopic analysis reference spectrum obtained from a kidney stone, showing differences with 1-methyl uric acid spectrum.

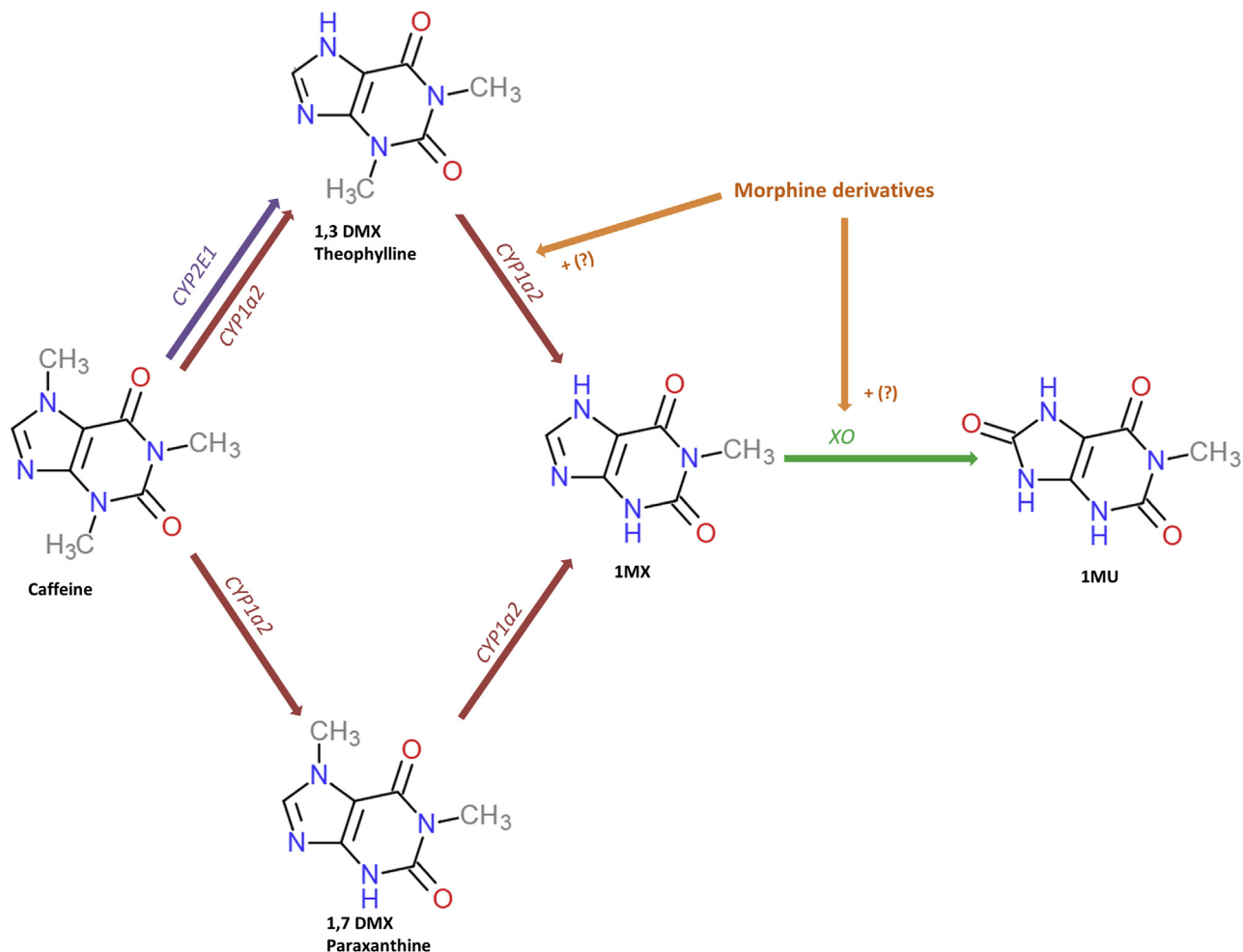


Figure 2. Main metabolites of caffeine found in the urine. XO, xanthine oxidase; CYP1A2, cytochrome P 450 1A2; 1,3 DMX, 1,3 dimethylxanthine (theophylline); 1,7 DMX, 1,7 dimethylxanthine; 1 MX, 1 methylxanthine; 1 MU, 1 methyluric acid.

Treatment and Outcome

Coffee and tea were restricted in cases 1 and 2. In case 1, aripiprazole dosage was halved. Her immunosuppressive protocol was switched to abatacept due to severe vascular lesions on the graft biopsy. Serum creatinine slowly decreased to baseline (98 $\mu\text{mol/l}$) 1 month after the biopsy. She had further serial kidney graft biopsy without persistent 1-methyluric acid crystals identified.

Case 2 received allopurinol and outcome was good (serum creatinine 95 $\mu\text{mol/l}$ 2 months after the diagnosis).

The evolution of case 3 is unknown.

DISCUSSION

These 3 cases of 1-methyluric acid nephropathy were characterized by severe acute kidney injury and in the 2 documented cases by tubular proteinuria and aseptic leukocyturia. Of note, no patient had pyelo-ureteral dilation or reported renal colic that could be related to kidney stones.

Crystalluria was performed in 1 case and revealed round-shaped 1-methyluric acid crystals with a central *maltese cross* under polarized light, quite similar to those described in the urine sediment of patients affected by 2-8 dihydroxyadenine nephropathy.⁵ Interestingly, white blood cells containing crystals were found in urine, suggesting that 1-methyluric acid crystals may induce innate immune cell response.

Kidney biopsies revealed acute tubular injury under optical light. However, the presence of intratubular cast on paraffin-embedded sections was inconstant, and more crystals were observed on frozen sections. Indeed, purine derivatives are sensitive to formaldehyde and may sometimes dissolve. In all cases, spectrometric analysis was mandatory to identify crystalline phases.

In cases 2 and 3, patients were drug addicts. Caffeine is transformed into 1-methyluric acid (and other metabolites) by cytochrome CYP1A2 and xanthine oxidase (Figure 2). Some studies have shown that both CYP1A2 and xanthine oxidase may be induced by morphine

and derivatives.^{S1,S2} Moreover, Ecstasy (3,4-methylenedioxymethamphetamine) street tablets and cocaine are frequently cut with several other compounds, particularly caffeine.^{S3} One may hypothesize that large caffeine intakes and potentially metabolic alteration due to morphine derivatives may promote 1-methyluric acid synthesis and acute kidney injury. By contrast, in case 1, there was no history of drug addiction reported or high caffeine consumption declared, and there is no evidence to date that aripiprazole may alter purine metabolism.

The outcome of 1-methyluric acid nephropathy seems good, after caffeine intake withdrawal (case 1 and 2) and xanthine oxidase inhibition by allopurinol (case 2). There is no evidence that xanthine oxidase inhibition by allopurinol or febuxostat may improve renal recovery, but considering 1-methyluric acid metabolism, it appears as a reasonable therapeutic option (Figure 2). In addition, urine alkalinization might be an interesting option to increase crystallite solubility, as classically performed in uric acid stone formers.

In conclusion, 1-methyluric acid nephropathy should be discussed in drug addicts affected by acute renal failure or when kidney biopsy (frozen sample) reveals the presence of polarizing crystals. Crystalluria also may be of help to identify atypical crystals in urine. In all cases, infrared spectroscopic analyses are essential for diagnosis.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Supplementary References.

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