Letter to the Editor

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Low-dose oral methotrexate-induced crystalluria

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To the Editor,

A 56-year-old man with psoriatic arthritis was prescribed oral methotrexate (15 mg each week every Sunday at around 13:00 UTC). No other relevant medication was administered. After 42 h, a routine control analysis was performed without significant abnormal results. Solely and surprisingly, a large number of crystals were observed in the urine sample in the absence of risk factors of drug-induced precipitation or other causes of crystal nephropathy, except an acidic pH of 5.5, the primary cause (along with volume depletion) of drug precipitation [1]. A possible, yet remote, cause points to a high intake of cola drinks during several days preceding the drug administration [2], as the patient has explicitly acknowledged. The capture of the images took place within the 90 min after micturition, and the spectral data throughout the same morning. One urine collected 10 weeks before and other three analyzed 3, 6 days and 7 weeks later showed no abnormalities, as well as no symptoms during urination. The sequence of analysis was as follows:

a) Ten weeks before (without treatment): Creatinine 71 $\mu\text{mol/L}$, eGFR(CKD-EPI) $>90 \text{ mL/min/1.73 m}^2$, albumin 46 g/L, urea 6.16 mmol/L, GGT 20 IU/L, sodium 144 mmol/L, potassium 4.6 mmol/L and erythrocyte count $4.52 \times 10^{12}/\text{L}$. Normal urine (negative results for elemental analysis), specific gravity 1025 and pH 5.5 (“Clinitek Atlas” analyzer, “Multistix Pro-10LS” strips [Siemens Healthcare, Tarrytown, NY, USA]). No crystals.

- b) On the same day that urine cloudy sediment (case study): Creatinine 73 $\mu\text{mol/L}$, eGFR $>90 \text{ mL/min/1.73 m}^2$, albumin 47 g/L, urea 8.16 mmol/L, GGT 21 IU/L, sodium 141 mmol/L, potassium 4.3 mmol/L and erythrocyte count $4.49 \times 10^{12}/\text{L}$. Normal urine (negative results for elemental analysis), specific gravity 1020 and pH 5.5.
- c) Three days after (continuing oral treatment): Normal urine (negative results for elemental analysis), specific gravity 1020 and pH 6.5. No crystals.
- d) Six days later (continuing oral treatment): Normal urine (negative results for elemental analysis), specific gravity 1025 and pH 6.5. No crystals.

The deposit was made up of a needle-shaped unit arranged in other three structures: (I) Toothpick-like elemental formation, (II) shell-like macle, (III) symmetric or asymmetric wheat-sheaf-like macle, and (IV) aggregates of the previous macles linked by the “isthmus/narrow” zone (Figure 1A). All these are strongly birefringent (Figure 1B, C). The basic shape of this polymorphic crystalline habit would be a “type-V solvatomorph of Chadha” ([3] see Figure 5f) in our patient. It has not been previously described.

The rarity of this precipitate made it necessary the positive identification to authenticate the nature of these crystals. A mass spectrometry (MS) procedure was used for this purpose [4]. The spectra confirm that this drug is the major component of the floccular, whitish and bulky precipitate appeared in the case urine of the patient (Figure 2A), as well as its “*in vivo*” metabolites (Figure 2B). To our knowledge, this is the first case positively confirmed of a urinary methotrexate precipitate in patients without intravenous administration [5–10].

Following seven weeks (continuing oral treatment), a new control analysis showed normal results again: Creatinine 70 $\mu\text{mol/L}$, eGFR $>90 \text{ mL/min/1.73 m}^2$, albumin 44 g/L, urea 4.66 mmol/L, GGT 17 IU/L, sodium 144 mmol/L, potassium 4.3 mmol/L and erythrocyte count $4.39 \times 10^{12}/\text{L}$. Normal urine (negative results for elemental analysis), specific gravity 1015 and pH 7.0 and absence of crystals. Furthermore, the lack of symptoms of acute renal impairment did not support a renal biopsy. This fact demonstrates the need for a skillful and more closely urine sediments even in low-dose treatment.

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Figure-1: Microscopic imaging. Light-microscopy images of urinary methotrexate crystals, where the four structures (I–IV quoted in the text) can be observed (A). Polarized light-microscopy image: (B) polarizer and analyzer placed at right angle and (C) nearly parallel (“DM-LSP” [Leica Microsystems, Wetzlar, Germany]).

Figure-2: Spectral data of the precipitate after washing and concentration steps.

(A) MS and MS/MS spectra (“4800 MALDI ToF/ToF MS” [AB-SCIEX, Framingham, MA, USA]) with the methotrexate ion-molecular peak ($m/z=456$; up, red arrow) and its defining fragments ($m/z=455.67$, 339.88 , 251.07 , 180.09 ; down, red asterisks). (B) MS peaks of “*in vivo*” metabolites ($m/z=325$: 2,4-diamino- N_{10} -methylpteroic acid (DAMPA) and $m/z=471$: 7-hydroxymethotrexate [7-OH-MTX]) resulting from additional spectral data, an unambiguous demonstration of the nature of this well formed crystalline habit.

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Ethical approval: Not applicable.

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