CASE REPORT

Urine Xanthine Crystals in Hematologic Malignancies with Tumor Lysis Syndrome

Shoko Ito¹, Shin-ichiro Fujiwara¹,², Tomoaki Yoshizawa³, Kaori Hayatsu³, Kaoru Sekiguchi¹, Rui Murahashi¹, Hirotomu Nakashima¹, Sae Matsuoka¹, Takashi Ikeda¹, Yumiko Toda¹, Shinichiro Kawaguchi¹, Takashi Nagayama¹, Kento Umino¹, Daisuke Minakata¹, Hiroyumi Nakano¹, Kaoru Morita¹, Ryoko Yamasaki¹, Masahiro Ashizawa¹, Chihiro Yamamoto¹, Kaoru Hatano¹, Kazuya Sato¹, Ken Ohmine¹ and Yoshinobu Kanda¹

Abstract:
Tumor lysis syndrome (TLS) is a metabolic disorder caused by massive tumor lysis. Hypouricemic agents are administered to prevent TLS-related hyperuricemia and renal failure. We experienced three cases of urine xanthine crystals during TLS in patients with hematologic malignancies who received prophylactic febuxostat. Yellowish and pinkish deposits were observed in urinary tract catheters and urinary bags. Urine microscopy revealed that the deposits were xanthine crystals. In rapid tumor lysis, inhibition of xanthine oxidase can cause xanthine accumulation and urine xanthine crystallization. During TLS, urine xanthine crystals may be overlooked, so careful observation and management are required to avoid xanthine nephropathy.

Key words: xanthine crystals, tumor lysis syndrome, febuxostat, allopurinol, rasburicase

(Intern Med 61: 3271-3275, 2022)
(DOI: 10.2169/internalmedicine.9332-22)

Introduction
Tumor lysis syndrome (TLS) is a life-threatening complication caused by massive tumor cell lysis and often occurs after cytotoxic therapy in patients with a high tumor burden and hematologic malignancies (1, 2). In TLS, a large number of intracellular metabolites are released into the systemic circulation, resulting in hyperkalemia, hyperphosphatemia, secondary hypocalcemia, and hyperuricemia. Overexcretion of uric acid into the urine can contribute to the precipitation of crystalline uric acid in the renal tubules, which causes acute uric acid nephropathy with acute kidney injury. Furthermore, hyperphosphatemia with calcium phosphate deposition in the renal tubules can cause acute kidney injury.

To prevent TLS, besides intravenous hydration and monitoring of urine output, hypouricemic agents, such as allopurinol and febuxostat, are widely used. These drugs competitively inhibit xanthine oxidase, which catalyzes the conversion of hypoxanthine and xanthine to uric acid (Fig. 1). However, they consequently increase serum and urine hypoxanthine and xanthine (3). There have been a few cases of urine xanthine crystallization and xanthine nephropathy caused by xanthine oxidase inhibitors during TLS in hematologic malignancies (4-8). However, the conditions under which xanthine crystallization occurs are still unclear.

We herein report three cases in which xanthine crystals were observed visually in urinary catheters during the management of TLS.

Case Reports
Case 1
A 57-year-old woman presented with an intraoral tumor and fatigue. Burkitt lymphoma was diagnosed, with bone marrow infiltration (76% of blast) and an oral and abdominal bulky mass. Laboratory data showed elevated lactate de-
hydrochloric acid, but were soluble in 10% KOH. Insoluble in 0.9% normal saline, 10% acetic acid, and 3% alike. A stone formation analysis revealed that 98% of the deposits decreased with continued administration of febuxostat. A rise uric acid level peaked on the fourth day and tended to level was elevated to 2.01 mg/dL on the fifth day. The se-
tal uric acid level peaked on the fourth day and tended to decrease with continued administration of febuxostat. A stone formation analysis revealed that 98% of the deposits consisted of xanthine crystals (Fig. 2E). The crystals were insoluble in 0.9% normal saline, 10% acetic acid, and 3% hydrochloric acid, but were soluble in 10% KOH.

Case 2
An 82-year-old man presented with abdominal pain. Diffuse large B-cell lymphoma was diagnosed using a computed tomography-guided biopsy of a tumor around the kidney. The LDH level was 466 U/L (upper limit of normal, 214 U/mL). He was diagnosed with stage IV disease and classified as being at high risk of TLS due to his LDH level and renal involvement. He received febuxostat 60 mg per day as prophylaxis for TLS and then received chemotherapy (cyclophosphamide 200 mg/m² for 5 days). On the second day, no xanthine crystals were found in the urine sediment. On the third day, however, manifestations of laboratory TLS, including hyperuricemia (10.4 mg/dL), hyperphosphatemia (11.6 mg/dL) and elevated serum creatinine (1.23 mg/dL), were observed along with the development of a yellowish deposit in the urinary tract catheter and urinary bag (Fig. 2B). The urine pH was 5.5, and metabolic acidosis was seen in the blood gases. The urine sediment contained brown, plate-like crystals (Fig. 2C, D) for 3 consecutive days, and the creatinine level was elevated to 2.01 mg/dL on the fifth day. The serum uric acid level peaked on the fourth day and tended to decrease with continued administration of febuxostat. A stone formation analysis revealed that 98% of the deposits consisted of xanthine crystals (Fig. 2E). The crystals were insoluble in 0.9% normal saline, 10% acetic acid, and 3% hydrochloric acid, but were soluble in 10% KOH.

Figure 1. Schematic illustration of purine metabolism.

Discussion
We experienced three cases with urine xanthine crystals in TLS under the use of febuxostat. Febuxostat was administered to prevent uric acid production by inhibiting xanthine oxidase, which can lead to urine xanthine accumulation and crystallization in the setting of rapid tumor lysis and massive release of nucleic acid.

During TLS, febuxostat increases urine hypoxanthine and xanthine concentrations; however, urine xanthine crystals are not widely recognized. A previous study showed that several types of crystals were detected by urine sediment in all 11 patients with chemotherapy-sensitive lymphomas who were receiving chemotherapy and allopurinol. Crystals, nonspecific but similar in morphology to xanthine crystals, were observed in eight patients, and absorbance peaks corresponding to xanthine were detected in four of the patients tested. In the present three cases, a urethral catheter was inserted for fluid management, which helped us detect the deposition, but urethral catheters are not systematically inserted in all cases of TLS. Furthermore, the serum and urine xanthine levels are not routinely measured, so clinicians are rarely aware of xanthine crystals in daily practice. Consequently, xanthine crystals may be overlooked, and there may be even more patients with xanthine crystals associated with TLS than previously considered.

In the present three cases, despite the use of febuxostat, serum uric acid levels tended to increase, and xanthine crystals were observed at that time. As previously reported, patients with xanthine crystals during TLS showed an increase in serum uric acid levels after chemotherapy, despite the
administration of allopurinol (5, 6). Elevated serum uric acid levels during the administration of xanthine oxidase inhibitors indicate far more massive tumor lysis in the body, which can exceed the solubility of hypoxanthine and xanthine in the urine. This is consistent with the disappearance of xanthine crystals for a few days after the decrease in serum uric acid levels in the present three cases. The assessment of the degree of tumor lysis, including changes in serum uric acid levels, is useful for predicting the formation of xanthine crystals.

Regarding elevated serum uric acid levels under the use of xanthine oxidase inhibitors, clinicians should consider replacing xanthine oxidase inhibitors with rasburicase to prevent xanthine crystal formation. However, among patients on prophylactic rasburicase and allopurinol, xanthine crystals have been observed in those with serum uric acid levels below the limit of detection (8), indicating that the presence of xanthine crystals must be kept in mind when using a xanthine oxidase inhibitor, even if the uric acid level is well-controlled by rasburicase. In terms of the risk of xanthine crystals, xanthine oxidase inhibitors may not be necessary under rasburicase administration.

Figure 2. A: Clinical course (Case 1). B: Photograph of xanthine crystals in the urine bag (Case 1). C: Photograph of xanthine crystals on urine microscopy ×100 (Case 1). D: Photograph of xanthine crystals in urine microscopy ×200 (Case 1). E: The analysis of stone formation (Case 1).
In the present study, renal failure was confirmed in two of three cases. Although no pathological evaluation was performed, a large number of crystals were thought to have precipitated within the renal tubules, consequently resulting in obstructive nephropathy. In a previous study, renal failure was observed in 4 of 11 patients with urine crystals after chemotherapy and allopurinol therapy (5). Conversely, patients with urine xanthine crystals during TLS did not present with renal failure in the other report (8). Furthermore, in 10 patients who received febuxostat for TLS prophylaxis, the urine xanthine concentration increased to the reported concentrations associated with xanthine nephropathy after chemotherapy, but there was no progress of renal impairment in any of the cases (3). These findings suggest that the number of xanthine crystals may contribute to the development of renal failure, but more cases will need to be accumulated to elucidate the relationship between xanthine crystals and xanthine nephropathy.

The present study has several limitations. First, our three cases were considered to be at high risk for TLS according to the consensus regarding TLS (2). Therefore, it may have been better to use rasburicase prophylactically or at the detection of an elevated uric acid level. Second, serum and urine xanthine levels were not measured in any of the three cases. The level at which xanthine crystallizes is an important issue in the investigation of the cause of xanthine crystallization. Third, febuxostat may be more likely to cause xanthine crystals than allopurinol. A randomized control trial showed that febuxostat significantly reduced the area under the concentration-time curve of uric acid compared to allopurinol in patients with hematologic malignancies at intermediate to high risk of TLS (9). Lower uric acid levels may result in increased xanthine levels in the serum and urine and consequent xanthine crystallization.

In conclusion, we reported three cases of urine xanthine crystals in patients with TLS receiving febuxostat. Urine xanthine crystals may be missed during TLS, and careful observation and management can help prevent xanthine nephropathy. Further studies will be needed to determine the optimal intervention for preventing TLS.

This study performed in accordance with the Declaration of Helsinki and its later amendments. Written informed consent was obtained from the patients for the publication of these case reports and any accompanying images. It was determined that this study did not require the approval of the Institutional Review Board of Jichi Medical University.
The authors state that they have no Conflict of Interest (COI).

References

1. Coiffier B, Altman A, Pui CH, Younes A, Cairo MS. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol 26: 2767-2778, 2008.

2. Cairo MS, Coiffier B, Reiter A, Younes A: TLS Expert Panel. Recommendations for the evaluation of risk and prophylaxis of tumour lysis syndrome (TLS) in adults and children with malignant diseases: an expert TLS panel consensus. Br J Haematol 149: 578-586, 2010.

3. Takai M, Yamauchi T, Ookura M, et al. Febuxostat for management of tumor lysis syndrome including its effects on levels of purine metabolites in patients with hematological malignancies - a single institution’s, pharmacokinetic and pilot prospective study. Anticancer Res 34: 7287-7296, 2014.

4. Band PR, Silverberg DS, Henderson JF, et al. Xanthine nephropathy in a patient with lymphosarcoma treated with allopurinol. N Engl J Med 283: 354-357, 1970.

5. Hande KR, Hixson CV, Chabner BA. Postchemotherapy purine excretion in lymphoma patients receiving allopurinol. Cancer Res 41: 2273-2279, 1981.

6. LaRosa C, McMullen L, Bakdash S, et al. Acute renal failure from xanthine nephropathy during management of acute leukemia. Pediatr Nephrol 22: 132-135, 2007.

7. Omokawa A, Oguma M, Ueki S, Saga T, Hirokawa M. Urine xanthine crystals in tumor lysis syndrome. Urology 120: e9-e10, 2018.

8. Ohnuma K, Koyabashi S, Jikimoto T, et al. Xanthine crystals in urine sediment of a patient who received chemotherapy for adult T-cell leukemia. Igaku Kensa (Jpn J Med Technol) 68: 763-768, 2019 (in Japanese).

9. Spina M, Nagy Z, Ribera JM, et al. FLORENCE: a randomized, double-blind, phase III pivotal study of febuxostat versus allopurinol for the prevention of tumor lysis syndrome (TLS) in patients with hematologic malignancies at intermediate to high TLS risk. Ann Oncol 26: 2155-2161, 2015.