Primary Tumor Infiltration and Severe Acute Kidney Injury in Patients with Acute Myeloblastic Leukemia

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In patients with hematologic malignancies, acute kidney injury (AKI) is the most common complication requiring nephrologist consultation. Although the causes of AKI are multifactorial, primary tumor infiltration is rare in patients with acute myeloblastic leukemia (AML). This makes it challenging to determine the cause of AKI and the optimal chemotherapy regimen for AML. We describe two cases of AML (French-American-British classification: M2, M4) in patients with AKI requiring hemodialysis. We successfully identified the cause of AKI as primary leukemic infiltration and started induction chemotherapy in the setting of hemodialysis. This treatment significantly improved renal function and resulted in AML remission. In this report, we describe several clinical characteristics of AKI due to primary tumor infiltration. In addition, we emphasize the importance of onconephrology, a new subspecialty concerned with the complex relationship between the kidneys and cancer.

(Key words: acute kidney injury, acute myeloblastic leukemia, tumor infiltration, onco-nephrology, chemotherapy)

**Introduction**

Among patients with hematologic malignancies, acute kidney injury (AKI) is the most common complication requiring nephrologist consultation\(^1\). The causes of AKI are multifactorial and are classified as cancer-specific and non-cancer-specific\(^2,3\). In primary tumor infiltration, a cancer-specific cause of AKI, immediate chemotherapy for AML is warranted in order to control AML, reduce tumor infiltration of the kidney, and facilitate recovery from AKI. However, primary tumor infiltration is less common in patients with acute myeloblastic leukemia (AML)\(^4,5\); therefore, appropriate diagnosis and management might be challenging. Onconephrology is a new subspecialty\(^6\) in which nephrologists address the complex relationship between the kidneys and cancer.

In this report, we discuss two patients with AML (French-American-British [FAB] classification: M2, M4) who presented with severe AKI. We describe the clinical characteristics of AKI due to tumor infiltration and treatment with induction chemotherapy in the setting of hemodialysis. In addition, we highlight the importance of onconephrology in identifying the optimal chemotherapy regimen for patients with severe AKI.

**Case Report**

**Case 1.** A 43-year-old woman was admitted to the hospital for abdominal pain of 1 month’s duration. On admission, laboratory analysis showed a white blood cell count of 18,700/μL (33% blasts) and a hemoglobin level of 9.1 mg/dL. A peripheral blood smear revealed numerous Auer bodies. Creatinine was 0.59 mg/dL, and urinalysis results were normal (Table 1). The patient was hospitalized in the department of hematology with suspected leukemia. Hematologists performed bone marrow aspiration and collected a biopsy specimen, which confirmed a diagnosis of AML (FAB: M2). On hospital day 3, she de-
veloped fever and dental infection was diagnosed. Chemotherapy was postponed and tazobactam/piperacillin and vancomycin were instead administered for the tooth infection. On day 5, creatinine level increased to 3.08 mg/dL. Her kidney function rapidly deteriorated, resulting in anuria.

The present nephrologists were consulted for AKI and started intermittent hemodialysis for anuria and investigated the cause of AKI. Vancomycin had been administered only once and was therefore not a likely cause of severe AKI. The patient had not received any other nephrotoxic medicine, such as nonsteroidal anti-inflammatory drugs, contrast enema, or amphotericin. Hypovolemia was excluded because of the absence of a history of vomiting, diarrhea, or bleeding. Fractional excretion of sodium and fractional excretion of urea nitrogen were consistent with renal AKI rather than pre-renal AKI. In particular, increase in urine β2-MG and NAG suggested severe tubular injury (Table 1). Laboratory data excluded the possibility of tumor lysis syndrome and uric acid nephropathy (Table 1). The results of additional immunological studies were unremarkable, and a blood culture was negative. Urine sediment revealed more than 100 white blood cells/high-power field without bacteria and more than 30 granular casts/high-power field. Abdominal computed tomography (CT) showed bilateral nephromegaly, with no evidence of hydronephrosis or a renal mass. Primary tumor infiltration of the kidneys was the suspected cause of AKI. On day 12, induction chemotherapy was initiated with idarubicin (12 mg/m²/day on days 1–3) and cytarabine (100 mg/m²/day on days 1–7) in the setting of hemodialysis. Chemotherapy significantly improved kidney function, and hemodialysis was discontinued on day 18 (Fig. 1).

Case 2. A 66-year-old woman received a diagnosis of AML (FAB: M4) 6 weeks before hospitalization. Initial laboratory data showed a white blood cell count of 90,700/μL (18% blasts). Chemotherapy with idarubicin (12 mg/m²/day on days 1–3) and cytarabine (100 mg/m²/day on days 1–7) was initiated. After chemotherapy, laboratory data showed a white blood cell count of 2,300/μL (0.5% blasts). Bone marrow aspiration revealed significant cyto-reduction in the blasts. The patient was re-hospitalized to receive consolidation chemotherapy. Table 1 shows the results of laboratory analysis. On hospital day 4, bone marrow aspiration revealed a 10% increase in blasts, which confirmed AML recurrence. On day 6, laboratory data revealed deterioration in kidney function, with a creatinine level of 2.96 mg/dL. Urine sediment revealed 50–99 white blood cells/high-power field, 30–49 granular casts/high-power field, and 50–99 epithelial casts/high-power field. We were consulted for AKI. The patient developed anuria and required renal replacement therapy. She had not received nephrotoxic drugs and maintained a euvolemic fluid status. Abdominal CT showed bilateral nephromegaly (Fig. 2). We concluded that AML recurrence had caused rapid progressive AKI due to tumor infiltration, as in case 1, and proposed re-induction chemotherapy. Although the initial chemotherapy regimen did not completely suppress AML, cyto-reduction was significant, and the same regime was thus selected. After re-induction chemotherapy, kidney function significantly improved and hemodialysis was discontinued (Fig. 1).

Discussion

Two patients with AML (FAB: M2, M4) presented with severe AKI requiring hemodialysis, which was caused by primary leukemic infiltration. To treat AML in patients receiving hemodialysis, we shared their pharmacokinetic data with hematologists. Induction chemotherapy successfully improved renal function and resulted in leukemia remission. Although primary leukemic infiltration is a rare cause of AKI, especially in M2 AML, clinicians need to be aware of this possibility and of the need to initiate optimal chemotherapy immediately.

In patients with hematologic malignancy, AKI is probably the most common kidney complication requiring nephrologist consultation. AKI, defined as a 50% increase in serum creatinine, developed in 36% of patients with AML or high-risk myelodysplastic syndrome. The causes of AKI are multifactorial and are categorized as cancer-specific and non-cancer-specific. Cancer-specific causes include tumor lysis syndrome, hemophagocytic syndrome, thrombotic microangiopathy, obstruction, and chemotherapy-induced renal injury; non-cancer-specific causes are volume depletion, sepsis, and nephrotoxic drugs such as nonsteroidal anti-inflammatory drugs, antibiotics, and contrast enema. Primary tumor infiltration is a much less common cause of AKI and was reported in only 1% of patients with acute leukemia. In AML, extramedullary leukemia is more likely to have a myelomonocytic morphology (FAB: M4, M5); therefore, AML with maturation (FAB: M2) and development of AKI from tumor infiltration have not been reported previously.

In this report, we emphasize several clinical characteristics important in the diagnosis of tumor infiltration. First, renal deterioration developed in patients with un-
Table 1 Clinical characteristics and laboratory results for the two patients

|                | Case 1                   | Case 2                   |
|----------------|--------------------------|--------------------------|
| Age, years     | 43                       | 66                       |
| Sex            | Female                   | Female                   |
| WHO classification | Acute myelomonocytic leukemia with maturation | Acute myelomonocytic leukemia |
| FAB classification | M2                       | M4                       |

| Laboratory data | Day 1 | Day 5 | Day 1 | Consultation day 5 | Day 6 | Consultation day 6 |
|-----------------|-------|-------|-------|--------------------|-------|--------------------|
| WBC             | 18,700| 25,800| 8,600 | 4,600              |       |                    |
| Stab            | 0.5   | 1.5   | 0.0   | 0.0                |       |                    |
| Seg             | 32.0  | 44.5  | 73.0  | 82.5               |       |                    |
| Lympho          | 21.5  | 16.5  | 9.0   | 6.5                |       |                    |
| Mono            | 0.0   | 0.5   | 11.5  | 5.0                |       |                    |
| Eosino          | 0.5   | 1.5   | 2.0   | 6.0                |       |                    |
| Baso            | 1.0   | 0.5   | 2.5   | 0.0                |       |                    |
| Blast           | 33.0  | 25.5  | 0.5   | (-)                |       |                    |
| Promyelo        | 0.5   | 0.5   | (-)   | (-)                |       |                    |
| Myelo           | 7.5   | 7.0   | 0.5   | (-)                |       |                    |
| Metamyel        | 3.5   | 2.0   | (-)   | (-)                |       |                    |
| Reticulocyte    | 6     | 7     | 43    | 12                 |       |                    |
| HGB             | 9.1   | 7.7   | 404   | 11                 |       |                    |
| PLT             | 69,000| 57,000| 343,000| 173,000           |       |                    |
| AST             | 48    | 49    | 16    | 16                 |       |                    |
| ALT             | 76    | 49    | 21    | 13                 |       |                    |
| Na              | 140   | 139   | 134   | 136                |       |                    |
| K               | 3.5   | 4.6   | 3.8   | 3.4                |       |                    |
| Ca              | 9.4   | 8.0   | 9.0   | 7.5                |       |                    |
| P               | 3.3   | 5.8   | 3.0   | 2.4                |       |                    |
| UA              | 4.3   | 5.4   | 4.5   | 5.2                |       |                    |
| Alb             | 4.1   | 3.2   | 4.1   | 2.3                |       |                    |
| BUN             | 6.8   | 21.5  | 14.9  | 32.6               |       |                    |
| Cr              | 0.59  | 3.08  | 0.74  | 2.96               |       |                    |

Urinalysis

|                | Day 1 | Day 5 | Day 6 |
|----------------|-------|-------|-------|
| Urine gravity  | 1.013 | 1.012 | 1.028 |
| pH             | 5.5   | 6.5   | 5.5   |
| Urine protein  | (-)   | (3+)  | (-)   |
| Hematuria      | (-)   | (1+)  | (-)   |
| Bacteria       | (-)   | (-)   | (-)   |
| White blood cell casts | 1-4  | >100  | 1-4   |
| Granular casts | (-)   | 30-49 | 10-19 |
| Waxy casts     | (-)   | 1-4   | (-)   |
| Epithelial casts | (-) | 50-99 | 10-19 |
| Urine protein  | NA    | 6.9   | NA    |
| Urine β2-MG    | NA    | 19,908| NA    |
| NAG            | NA    | 63.3  | NA    |
| FENa           | NA    | 2.2   | NA    |
| FEUN           | NA    | 41.8  | NA    |

Day 1 is the day of hospitalization, and days 5 and 6 are the consultation days for cases 1 and 2, respectively.

Abbreviations: Alb, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; β2-MG, β2-microglobulin; Cr, creatinine; FAB, French-American-British classification; FENa, fractional excretion of sodium; FEUN, fractional excretion of urea nitrogen; FLT, FMS-related tyrosine kinase; Hb, hemoglobin; Ht, hematocrit; ITD, internal tandem duplication; LDH, lactate dehydrogenase; NA, not assessed; NAG, N-acetyl-beta-glucosaminidase; Plt, platelet; UA, uric acid; RBC, red blood cell; WBC, white blood cells; WHO, World Health Organization
Case 1

The patient was hospitalized for suspected acute leukemia. Antibiotics were administered for fever after hospitalization. VCM was administered only on day 1. On day 5, creatinine increased from 0.59 to 3.08 mg/dL. Renal dysfunction had progressed rapidly, and the patient required renal replacement therapy. Intermittent hemodialysis was introduced. After investigation, we concluded that primary tumor infiltration was the most likely cause of AKI. On day 12, induction chemotherapy with idarubicin (12 mg/m²/day on days 1-3) and cytarabine (100 mg/m²/day on days 1-7) was initiated in the setting of hemodialysis.

Case 2. Bone marrow aspiration performed before chemotherapy indicated AML recurrence. On day 6, creatinine increased from 0.74 to 2.96 mg/dL. The patient had not received any nephrotoxic drug. As in Case 1, tumor infiltration was thought to be the cause of AKI. On day 7, reinduction chemotherapy with idarubicin (12 mg/m²/day on days 1-3) and cytarabine (100 mg/m²/day on days 1-7) was introduced.

In both cases, full-dose induction chemotherapy significantly improved renal function and led to remission of AML. Hemodialysis was discontinued after renal recovery.

Abbreviations: AKI, acute kidney injury; AML, acute myeloblastic leukemia; Ara C, cytarabine; Cr, creatinine; HD, hemodialysis; IDA, idarubicin; PIPC, piperacillin; UV, urine volume; TAZ, tazobactam; and VCM, vancomycin.

Fig. 1 Clinical course
Kidney Injury Due to Tumor Infiltration

Both kidneys were enlarged at AKI onset. There was no hydronephrosis or renal mass. Kidney size normalized upon AML remission.

Abbreviations: AML, acute myeloblastic leukemia; CT, computed tomography.

Few studies have investigated dose modification of anticancer drugs in patients who develop AKI requiring hemodialysis. Normally, the kidneys excrete drugs by glomerular filtration, tubular secretion, and tubular reabsorption. However, various factors affect drug pharmacokinetics in persons with renal insufficiency, and drug removal by dialysis depends on many factors, such as the drug characteristics and the type of dialysis and equipment used. The standardized induction chemotherapy regimen for AML is idarubicin and cytarabine, which are metabolized in the liver. The molecule size and protein binding rate are 533.95 kilodaltons and 97%, respectively, for idarubicin and 243.22 kilodaltons and 13% for cytarabine. Idarubicin is non-dialyzable because of its large molecular size and high protein binding rate. In contrast, cytarabine is a small molecule and has a low protein binding rate; however, its large volume distribution (2–3 L/kg) makes it less likely to be dialyzed. In addition, cytarabine elimination is more likely to rely on tubular secretion. We believe that, to provide appropriate treatment, clinicians need to fully understand the pharmacokinetic characteristics of cancer-targeted drugs.

Onconephrology is a new subspecialty that aims to improve treatment outcomes by focusing on the complex relationship between the kidneys and cancer. Cancer can cause a variety of renal diseases. In addition, recently developed anticancer chemotherapy agents, such as immune checkpoint inhibitors, might cause kidney injury. Therefore, to appropriately care for patients with cancer and kidney injury, nephrologists and oncologists must share specialized knowledge, techniques, and experience.

In conclusion, primary tumor infiltration caused severe AKI in two patients with AML (FAB: M2, M4), and in-
duction chemotherapy in the setting of hemodialysis restored renal function and improved AML. Outcomes for patients with hematologic malignancies and kidney diseases are likely to be improved by increased training in onconephrology.

Conflict of Interest: The authors declare no competing financial interests.

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