—Case Reports—

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 kidney 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.
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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-

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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/m^2/day on days 1–3) and cytarabine (100 mg/m^2/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 of 90,700/μL (18% blasts). Chemotherapy with idarubicin (12 mg/m^2/day on days 1–3) and cytarabine (100 mg/m^2/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 cytoreduction 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, cytoreduction 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[1]. 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[2,7,8]. Primary tumor infiltration is a much less common cause of AKI[2,8,9] and was reported in only 1% of patients with acute leukemia[10]. In AML, extramedullary leukemia is more likely to have a myelomonocytic morphology (FAB: M4, M5)[4,5,11]; 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		
	Day 1	Consultation (day 5)	Day 1	Consultation (day 6)	
Laboratory data					
WBC	18,700	25,800	8,600	4,600	/μL
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	g/dL
PLT	69,000	57,000	343,000	173,000	/μL
AST	48	49	16	16	IU/L
ALT	76	49	21	13	IU/L
Na	140	139	134	136	mEq/L
K	3.5	4.6	3.8	3.4	mEq/L
Ca	9.4	8.0	9.0	7.5	mg/dL
P	3.3	5.8	3.0	2.4	mg/dL
UA	4.3	5.4	4.5	5.2	mg/dL
Alb	4.1	3.2	4.1	2.3	g/dL
BUN	6.8	21.5	14.9	32.6	mg/dL
Cr	0.59	3.08	0.74	2.96	mg/dL
Urinalysis					
Urine gravity	1.013	1.012	1.028	1.019	
pH	5.5	6.5	5.5	6.5	
Urine protein	(-)	(3+)	(-)	(3+)	
Hematuria	(-)	(1+)	(-)	(2+)	
Bacteria	(-)	(-)	(-)	(-)	
White blood cell casts	1-4	>100	1-4	50-99	/HPF
Granular casts	(-)	30-49	10-19	>100	/HPF
Waxy casts	(-)	1-4	(-)	20-29	/HPF
Epithelial casts	(-)	50-99	10-19	20-29	/HPF
Urine protein	NA	6.9	NA	4.7	mg/dL
Urine β2-MG	NA	19,908	NA	29,138	ug/L
NAG	NA	63.3	NA	63.3	U/L
FENa	NA	2.2	NA	2.1	%
FEUN	NA	41.8	NA	44.1	%

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

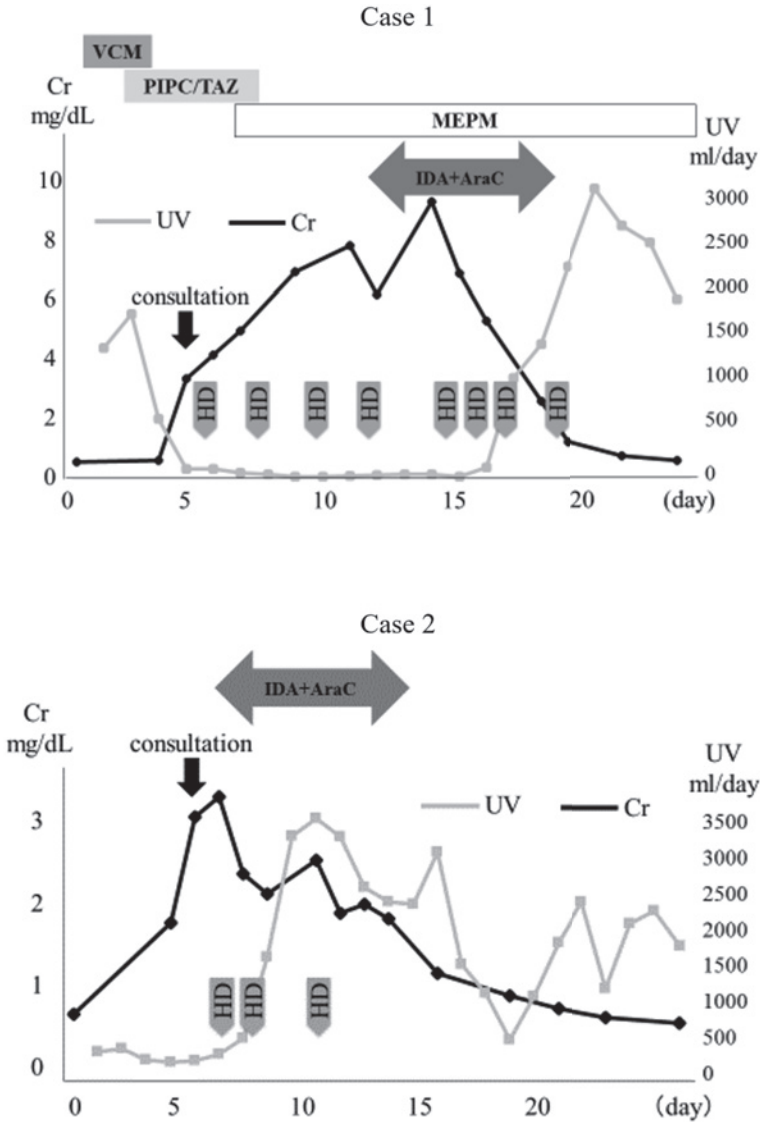

Fig. 1 Clinical course

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/m^2/day on days 1-3) and cytarabine (100 mg/m^2/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/m^2/day on days 1-3) and cytarabine (100 mg/m^2/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.

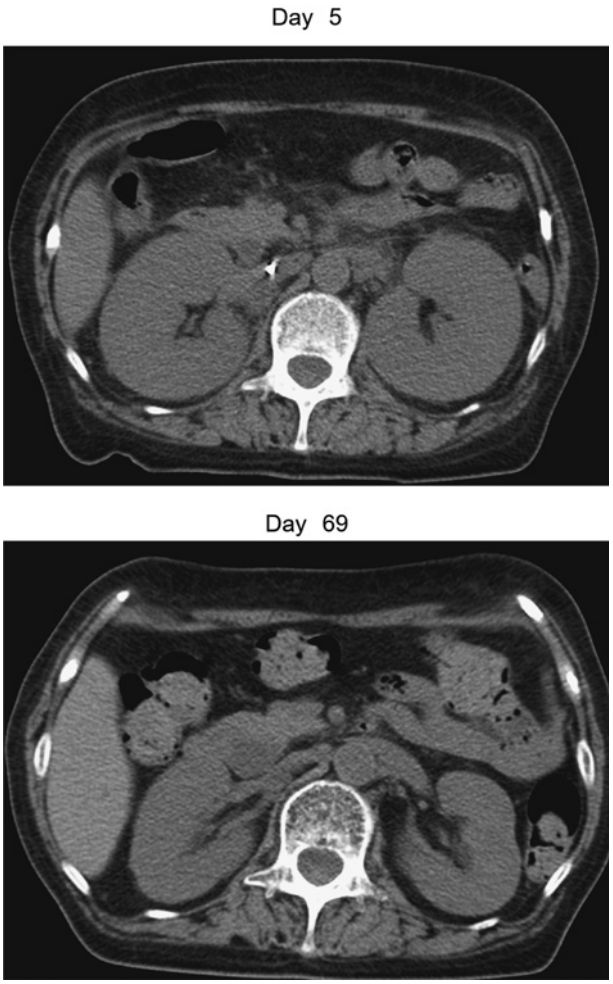

Fig. 2 Abdominal CT
Both kidneys were enlarged at AKI onset. There was no hydronephrosis or renal mass. Kidney size normalized upon AML remission.
Abbreviations: AML, acute myeloblastic leukemia; CT, computed tomography.

treated or recurrent AML. A previous study reported that, before chemotherapy was initiated, renal failure was more likely to be related to proliferation of leukemic blasts[12]. Clinicians need to consider leukemic proliferation, regardless of leukemia type, as an important cause of AKI in the early course of the disease. Second, urine sediment was useful for determining the cause of the disease. The presence of numerous white blood cells without bacteria and granular casts indicated a tubulointerstitial pattern of renal injury and leukemic infiltration. The pathophysiological mechanism of renal dysfunction by tumor infiltration was reported to involve acute tubular compression and disruption of the kidney microvasculature, due to increased interstitial pressure, which contributed to renal failure[3]. In our patients, we believe that infiltrating leukemic cells completely occluded the tubular lumen in both kidneys and subsequently increased hydraulic pressure in the lumen. Increased hydraulic pressure in the lumen decreased glomerular filtration rate, which is governed by gradients of hydraulic pressure between the glomerular capillaries and Bowman's space[13]. Third, we initiated induction chemotherapy before renal biopsy. Although percutaneous kidney biopsy might have confirmed the diagnosis[14], bleeding risk is substantial in patients receiving hemodialysis. Analysis of the risks and benefits indicated that it was reasonable to initiate induction chemotherapy before histological confirmation of the diagnosis. Urine cytology might be a useful alternative to renal biopsy, although its sensitivity is relatively low. The subsequent rapid recovery of renal function and kidney size associated with AML remission confirmed that the cause of AKI was primary tumor infiltration.

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[15], 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[16]. In addition, cytarabine elimination is more likely to rely on tubular secretion[17]. 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[18,19]. 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.

References

1. Lahoti A, Kantarjian H, Salahudeen AK, et al. Predictors and outcome of acute kidney injury in patients with acute myelogenous leukemia or high-risk myelodysplastic syndrome. Cancer. 2010;116:4063–8.
2. Canet E, Zafrani L, Lambert J, et al. Acute kidney injury in patients with newly diagnosed high-grade hematological malignancies: impact on remission and survival. PLoS One. 2013;8:e55870.
3. Luciano RL, Brewster UC. Kidney involvement in leukemia and lymphoma. Adv Chronic Kidney Dis. 2014;21:27–35.
4. Duda J, Zoger S. Presentation of M4 acute myeloid leukemia in anuric renal failure with hyperuricemia and enlarged kidneys. J Pediatr Hematol Oncol. 2002;24:55–8.
5. Tapper EB, Luptakova K, Joyce RM, Tzachanis D. A 78-year-old man with acute myeloid leukemia (AML) and acute renal failure. Am J Case Rep. 2014;15:364–7.
6. Kitai Y, Matsubara T, Yanagita M. Onco-nephrology: current concepts and future perspectives. Jpn J Clin Oncol. 2015;45:617–28.
7. Soares M, Salluh JI, Carvalho MS, Darmon M, Rocco JR, Spector N. Prognosis of critically ill patients with cancer and acute renal dysfunction. J Clin Oncol. 2006;24:4003–10.
8. Darmon M, Thiery G, Ciroldi M, Porcher R, Schlemmer B, Azoulay É. Should dialysis be offered to cancer patients with acute kidney injury? Intensive Care Med. 2007;33:765–72.
9. Abudayyeh AA, Lahoti A, Salahudeen AK. Onconephrology: the need and the emergence of a subspecialty in nephrology. Kidney Int. 2014;85:1002–4.
10. Lundberg WB, Cadman ED, Finch SC, Capizzi RL. Renal failure secondary to leukemic infiltration of the kidneys. Am J Med. 1977;62:636–42.
11. Rüger W, Kruip MJ, Betjes MG. Reversible renal failure due to bilateral renal sarcoma in a patient with acute myeloid leukemia. Ren Fail. 2009;31:606–9.
12. Munker R, Hill U, Jehn U, Kolb HJ, Schalhorn A. Renal complications in acute leukemias. Haematologica. 1998; 83:416–21.
13. Harris RH, Gill JM. Changes in glomerular filtration rate during complete ureteral obstruction in rats. Kidney Int. 1981;19:603–8.
14. Vankalakunti M, Rohan A, Vishwanath S, et al. Spectrum of renal involvement in hematolymphoid neoplasms: Renal biopsy findings of 12 cases. Indian J Nephrol. 2015;25: 201–5.
15. A systematic collaborative overview of randomized trials comparing idarubicin with daunorubicin (or other anthracyclines) as induction therapy for acute myeloid leukaemia. AML Collaborative Group 1998. Br J Haematol. 1998; 103:100–9.
16. Bennett WM, Aronoff GR, Morrison G, et al. Drug prescribing in renal failure: dosing guidelines for adults. Am J Kidney Dis. 1983;3:155–93.
17. Lam YW, Banerji S, Hatfield C, Talbert RL. Principles of drug administration in renal insufficiency. Clin Pharmacokinet. 1997;32:30–57.
18. Cosmai L, Porta C, Gallieni M, Perazella MA. Onconephrology: a decalogue. Nephrol Dial Transplant. 2016; 31:515–9.
19. Kunitoh H. Top 10 reasons why you must learn onconephrology. Jpn J Clin Oncol. 2016;46:2–3.

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