FULL LENGTH ARTICLE

Acute Myeloid Leukemia Presenting Less Than 3 Weeks After Living Donor Kidney Transplant: A Case Report

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ABSTRACT

Acute myeloid leukemia (AML) is a rare malignancy with increased incidence in the kidney transplantation (KT) population for which immunosuppression has been implicated as a putative cause. The average time interval from KT to AML development is 5 years. We present the case of a 61-year-old man who was found to have peripheral blood blasts on a postoperative day 20 routine blood draw after an uneventful unrelated living donor kidney transplant. He subsequently had a bone marrow biopsy and next-generation sequencing (NGS)-based molecular testing, which demonstrated AML characterized by *SMC1A* and *TET2* mutations. He received induction chemotherapy followed by hematopoietic cell transplantation (HCT) from the kidney donor, who happened to be matched at one haplotype. At 12 months after his HCT and 15 months after his KT, his AML remained in remission, normal renal function was preserved, no active graft-versus-host disease was present, and immunosuppression was tapering. With full donor-derived hematopoietic chimerism, we expect to be able to discontinue immunosuppression shortly, thereby achieving tolerance. The short time interval between KT and development of AML suggests the malignancy was likely present before KT. Modern NGS-based analysis offers a promising method of identifying transplant candidates with unexplained hematologic abnormalities on pre-KT testing who may benefit from formal hematologic evaluation.

ACUTE myeloid leukemia (AML) accounts for approximately 80% of all acute leukemias in United States adults, with an average 5-year survival of 27% [1]. The individual prognosis from AML depends largely on its cytogenetic and molecular characteristics, with unfavorable features such as a complex karyotype or high-risk mutations conferring a significantly lower 5-year survival of 11% to 15% [2]. In the proposed pathogenesis of AML, immune evasion plays an important role in its ability to develop malignancy potential [3]. This is concordant with observations that AML, like other malignancies, has a higher incidence in the immunosuppressed population and often improves with immunomodulation [4,5].

The solid organ transplant population presents a uniquely vulnerable patient population given their usual need for life-long immunosuppression. Although AML is a relatively rare post-transplant malignancy, its incidence in post−kidney transplant (KT) patients remains 3- to 5-fold higher than in the general population [6-8]. Interestingly, the overwhelming majority of reported cases of post-KT AML have occurred years after KT, with the earliest reported case post-KT at 6 months [9]. Furthermore, to date, no case has been reported of AML occurring after a living donor KT (LDKT). We present the unique case of newly

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Table 1. HLA Type of Kidney Transplant Recipient and Donor Demonstrating a Single Haplotype Match (at Allele 1)

Recipient Locus	Allele 1	Allele 2	Donor Locus	Allele 1	Allele 2
A	01:01:01G	02:01:01G	A	01:01:01G	25:01:01G
B	08:01:01G	08:01:01G	B	08:01:01G	51:01:01G
C	07:01:01G	07:01:01G	C	07:01:01G	12:03:01G
DRB1	03:01:01G	03:01:01G	DRB1	03:01:01G	07:01:01G
DRQB1	02:01:01G	02:01:01G	DRQB1	02:01:01G	02:01:01G

diagnosed AML less than 3 weeks after LDKT in which the patient subsequently received hematopoietic cell transplantation (HCT) from his kidney donor.

CASE PRESENTATION

A 61-year-old man developed end-stage renal disease (ESRD) secondary to diabetes mellitus and hypertension, requiring hemodialysis. After completing his KT recipient evaluation, he was approved for KT. A 61-year-old man with no medical history, who was the patient's high school friend, was found to be a suitable kidney match and approved for donation. Interestingly, the donor and recipient were matched at a single haplotype (Table 1). The induction immunosuppression included alemtuzumab and a rapidly tapered course of prednisone; the recipient was maintained on mycophenolate and tacrolimus therapy (goal trough: 8-10 ng/mL). His postoperative course was unremarkable. He was discharged on postoperative day (POD) 4 with immediate graft function and a down-trending creatinine value of 2.0 mg/dL.

As an outpatient, he continued to make progress, with an improving glomerular filtration rate. He developed a superficial surgical site infection, which received local packing. On POD 20, he was found to have leukopenia and 1440 circulating blast cells/μL (61% blasts) on routine laboratory testing. The only symptom he was experiencing was fatigue, which was attributed to his KT recovery. He was admitted to the hospital for further testing, peripheral blood flow cytometry demonstrated the blasts to be of myeloid lineage (Fig 1A), and a bone marrow

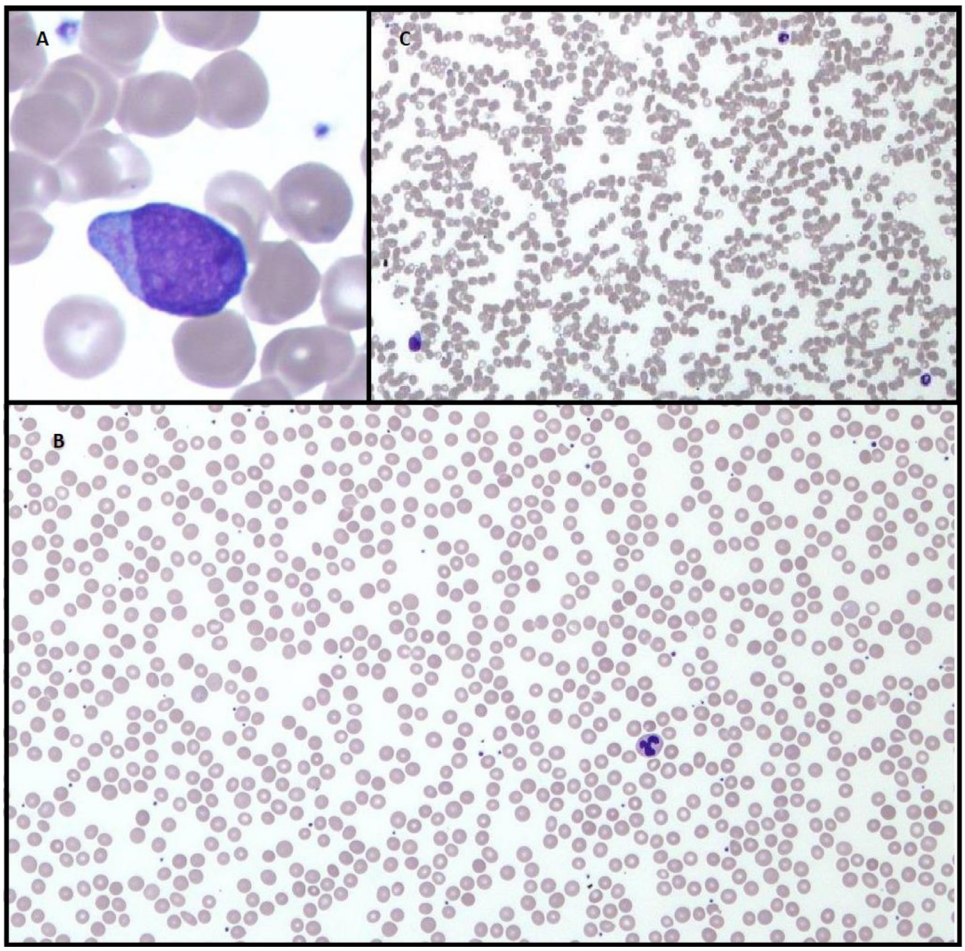

Fig 1. (A) Peripheral blood smear on postoperative day (POD) 22, at high power (1000 $\times$), showing a myeloblast with slender, reddish-colored Auer rods. **(B)** Peripheral blood smear prepared from sample obtained on POD 1 showing 2 polymorphonuclear neutrophils and 1 larger mononuclear cell (100 $\times$; thick part of smear because of leukopenia, where vanishingly rare blasts were identified). **(C)** Peripheral blood smear prepared from sample collected on POD 1 showing leukopenia with 1 mature neutrophil at low power field (200 $\times$).

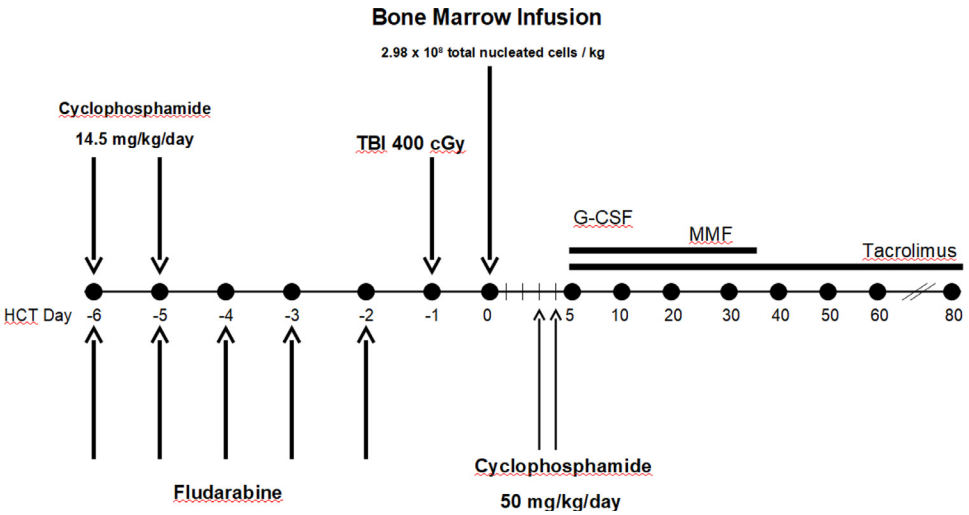

Fig 2. Schematic of hemopoietic stem cell treatment. G-CSF, granulocyte colony-stimulating factor; MMF, mycophenolate mofetil; TBI, total body irradiation.

biopsy was performed confirming the diagnosis of AML. Cytogenetic studies revealed trisomy 8, and next-generation sequencing (NGS) testing identified point mutations in *SMC1A* and *TET2*. He was started on induction treatment with the combination of venetoclax and decitabine on POD 26. His treatment course was complicated by pancytopenia requiring expected transfusional support. Mycophenolate was eliminated from his immunosuppression regimen, and he was started on oral prednisone 5 mg/d, in addition to continuing tacrolimus with a target level of 5 to 10 ng/mL. After hematopoietic recovery, bone marrow biopsy on POD 49 demonstrated complete remission, characterized by trilineage hematopoiesis, erythroid hyperplasia with a rare ringed sideroblast, several dyspoietic megakaryocytes, and 2% to 3% blasts whose phenotype could not be distinguished from that of normal regenerative elements. He was discharged on POD 54 with plans for additional cycles of decitabine and venetoclax chemotherapy.

He was subsequently evaluated for HCT given his older age and intermediate cytogenetic and molecular features. Given that his kidney donor was matched at a single haplotype, the decision was made to perform HCT using the same donor in hopes of not only achieving durable remission for AML but also immunologic tolerance for his transplanted kidney with a goal to be able to discontinue systemic immunosuppression without the risk for rejection. He was subsequently admitted for reduced-intensity conditioning comprising fludarabine, cyclophosphamide, and 400 cGy of total body irradiation, followed by mismatched unrelated donor bone marrow transplant consisting of 2.98×10^8 total nucleated cells/kg from his kidney donor on POD 127 relative to KT. Tacrolimus was stopped on day −3 of HCT, and prednisone 5 mg/d was continued. Prophylaxis for graft-versus-host disease was employed with high-dose posttransplant cyclophosphamide, tacrolimus, and mycophenolate (Fig 2). By day ±20 after HCT, he demonstrated donor engraftment with 100% full donor chimerism in unsorted peripheral blood cells. His post-HCT course was rather uneventful, and he was discharged on day +21 after HCT. At his most recent follow-up 12 months after HCT, he remained in complete remission with normal renal function, no evidence of active acute or chronic graft-versus-host disease, and complete immunosuppression withdrawal 6 months after the HCT. He maintained 100% full donor chimerism at 57 and 131 days post-HCT.

DISCUSSION

Immunosuppression after KT has been shown to cause a myriad of hematologic abnormalities, which usually can be detected on routine posttransplantation blood tests. One of the more serious conditions is therapy-related myelodysplastic syndrome (MDS), of which roughly one third will progress to AML [10]. Development of MDS after KT takes on average 3 to 5 years [11]. Similarly, the reported average time to onset of immunotherapy-related AML is about 5 years [12]. In this case, we detected AML on routine bloodwork only 20 days after LDKT, implying that the patient had indolent MDS or AML before KT, rather than developing the case de novo.

This case raises the important question of whether AML or other conditions, such as MDS, can be detected or should be screened for during evaluation of potential KT candidates. A detected malignancy in the pre-KT evaluation, such as AML, is a contraindication to KT and would have precluded this patient from undergoing routine KT. The majority of AML cases manifest with leukocytosis, neutropenia, and thrombocytopenia and clinically manifest with an infection or petechial hemorrhage at the time of diagnosis. However, a small minority of myeloid leukemias (fewer than 5%) will have a subtle "aleukemic" presentation, with relative preservation of hematopoiesis and only very subtle changes [13].

Such cases may evade detection by even the most sophisticated automated differential analyzers. Our patient had a routine complete blood count with differential performed by a

commercial laboratory 6 days before KT. Aside from a minimal normocytic anemia (hemoglobin 12.5 g/dL, mean corpuscular volume 95.6 fL, red cell distribution width 14.3%), which was attributed to the patient's ESRD, the only significant abnormality was a leukopenia of 2000 cells/μL (normal range, 3800 to 10,800 cells/μL). Automated differential revealed a proportional decrease of granulocytes and lymphocytes but failed to trigger any warnings that would have prompted further investigation. In the population with ESRD, such hematologic abnormalities are not uncommon [14]. Indeed, prior studies have demonstrated leukopenia in 16.7% of patients with ESRD [15]. In our patient, his low white blood cell count was also attributed to a recent viral illness from which he had recovered.

Interestingly, the first inpatient complete blood count on POD 1, performed on a Sysmex XN analyzer (Lincolnshire, IL, United States), raised instrument flags for cytopenias and red blood cell morphology. A blood film was prepared for technologist review and manual differential, but there were no specific "blast" warnings triggered. On the patient's re-presentation with AML 2 weeks after his discharge, the peripheral smear from the POD 1 was retrospectively reviewed. Overall, the slide was remarkable for leukopenia and mild thrombocytopenia with a preponderance of mature neutrophils (Fig 1B). However, when intentionally scanning thicker portions of the smear, vanishingly rare blast forms with nuclei invaginations and slender Auer rods (Fig 1C) were identified that obviously had escaped detection on routine manual differential from the optimal portion of the slide.

Although leukopenia has many benign causes, such as viral infections, medications, and chronic kidney failure, our case suggests that such laboratory findings potentially warrant further scrutiny because they could represent a primary hematologic disorder. Patients with early MDS may demonstrate leukopenia without any morphologic or cytogenetic abnormalities on bone marrow examination [16]. However, with the advent of NGS, tier I mutations of low allelic frequency, similar to those identified in this patient, may provide an early indication of evolving neoplasia. Such patients are now designated as having clonal hematopoiesis of indeterminate potential (CHIP) [17]. It is hypothesized that such individuals may be at higher risk for developing MDS or AML and thus warrant closer clinical surveillance than patients whose NGS testing does not reveal a CHIP mutation. However, in the relatively short period during which NGS testing has been widely available and clinically deployed, it has also become evident that many of these patients will not progress to overt myeloid neoplasia. It is certainly premature to assert whether discovering a CHIP mutation in pre-KT patients undergoing hematologic evaluation for cytopenia should preclude transplantation in the absence of more traditional indicators of myeloid neoplasm (eg, morphologic changes, increased blasts, or cytogenetic abnormalities) [18,19].

To our knowledge, no study or series has been published describing the effect of post-KT immunosuppression on patients who harbor CHIP mutations. In theory, immunosuppression would increase the rate of progression to MDS or AML by decreased immune surveillance, but this is entirely speculative. There are currently no guidelines regarding screening for AML or other hematologic malignancies during the KT evaluation process. In patients found to have asymptomatic cytopenias of unclear clinical significance, however, NGS analysis may offer a method of risk stratifying patients who are more likely to develop MDS or AML, prompting a formal evaluation by a hematologist before clearance for KT or increased surveillance practices afterward. At present, there is a paucity of data to guide the selection of patients who should receive NGS testing, and whether the potential benefit of uncovering a premalignant hematologic disorder outweighs the risks associated with the delay, and possible exclusion, of KT in patients who may never progress to develop an overt myeloid neoplasm even in the immunosuppressed state.

Our case presents a unique clinical scenario in transplantation. It is important to identify that he has had a favorable outcome thus far because of the incredible generosity and altruism of his life-long friend and living donor, who remarkably was a single haplotype match and agreed to donate both his kidney and bone marrow. Although small series have described success in combined bone marrow−kidney transplantation from matched related donors [20], and more recently haploidentical donors [21], these approaches remain experimental and difficult to generalize.

REFERENCES

[1] Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, editors. SEER cancer statistics review, 1975-2016. Based on November 2018 SEER data submission. Bethesda, MD: National Cancer Institute; 2019. https://seer.cancer.gov/csr/1975_2016/ [accessed March 24, 2021].

[2] Cornell R, Palmer J. Adult acute leukemia. Dis Mon 2012; 58:219–38.

[3] Teague R, Kline J. Immune evasion in acute myeloid leukemia: current concepts and future directions. J Immunother Cancer 2013;1:13.

[4] Sampaio M, Cho Y, Qazi Y, Bunnapradist S, Hutchinson I, Shah T. Posttransplant malignancies in solid organ adult recipients. Transplantation 2012;94:990–8.

[5] Hall E, Pfeiffer R, Segev D, Engels E. Cumulative incidence of cancer after solid organ transplantation. Cancer 2013;119:2300–8.

[6] Goldfarb D. Cancer after kidney transplantation in the United States. J Urol 2004;172(6 Part 1):2504–5.

[7] Kasiske B, Snyder J, Gilbertson D, Wang C. Cancer after kidney transplantation in the United States. Am J Transplant 2004;4:905–13.

[8] Morton L, Gibson T, Clarke C, Lynch C, Anderson L, Pfeiffer R, et al. Risk of myeloid neoplasms after solid organ transplantation. Leukemia 2014;8:2317–23.

[9] Manohar S, Sathick I, Grande J, El-Zoghby Z, Leung N. An unusual case of acute myeloid leukemia cell infiltration of the renal allograft: a case report and review of literature. Transplant Proc 2017;49: 1578–82.

[10] Tefferi A, Vardiman J. Myelodysplastic syndromes. N Engl J Med 2009;36:1872–85.

[11] Bhatia S. Therapy-related myelodysplasia and acute myeloid leukemia. Semin Oncol 2013;40:666–75.

[12] Rashidi A, Fisher S. Acute myeloid leukemia following solid organ transplantation: entity or novelty? Eur J Haematol 2014;92:459–66.

[13] Lowenberg B, Downing J, Burnett A. Acute myeloid leukemia. N Engl J Med 1999;341:1051–62.

[14] Suresh M, Mallikarjunareddy N, Singh S, Bandi H, Keerthi S, Chandrasekhar M. Hematological changes in chronic renal failure. Int J Sci Res 2012;2:1–4.

[15] Eswari V. Evaluation of hematological profile in chronic kidney disease patients in a tertiary care center, Kanchipuram: a cross sectional study. J Med Sci Clin Res 2018;6:677–83.

[16] Bennett J, Orazi A. Diagnostic criteria to distinguish hypocellular acute myeloid leukemia from hypocellular myelodysplastic syndromes and aplastic anemia: recommendations for a standardized approach. Haematologica 2009;94:264–8.

[17] Steensma DP, Bejar R, Jaiswal S, Lindsley RC, Sekeres MA, Hasserjian RP, Ebert BL. Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes. Blood 2015;126:9–16.

[18] Heuser M, Thol F, Ganser A. Clonal hematopoiesis of indeterminate potential. Dtsch Arztebl Int 2016;113:317–22.

[19] Young AL, Tong RS, Birmann BM, Druley TE. Clonal hematopoiesis and risk of acute myeloid leukemia. Haematologica 2019; 104:2410–7.

[20] Spitzer TR, Tolkoff-Rubin N, Cosimi AB, et al. Twenty-year follow-up of histocompatibility leukocyte antigen-matched kidney and bone marrow cotransplantation for multiple myeloma with end-stage renal disease: lessons learned. Transplantation 2019; 103:2366–72.

[21] Chen YB, Elias N, Heher E, et al. Haploidentical hematopoietic cell and kidney transplantation for hematological malignancies and end-stage renal failure. Blood 2019;134: 211–5.