

Correspondence

Piers Blombery, Peter MacCallum Cancer Centre,
Melbourne, Victoria, Australia.
Email: piers.blombery@petermac.org

ORCID

Piers Blombery  <https://orcid.org/0000-0002-9902-0022>
Georgina L. Ryland  <https://orcid.org/0000-0002-4990-0961>
Lucy C. Fox  <https://orcid.org/0000-0002-3855-8232>
Ella R. Thompson  <https://orcid.org/0000-0001-5206-5111>

REFERENCES

1. Palles C, Chew E, Grolleman JE, Galavotti S, Flensburg C, Jansen EAM, et al. Germline loss-of-function variants in the base-excision repair gene MBD4 cause a mendelian recessive syndrome of adenomatous colorectal polyposis and acute myeloid leukaemia. *bioRxiv*. 2021. <https://doi.org/10.1101/2021.04.27.441137>
2. Sanders MA, Chew E, Flensburg C, Zeilemaker A, Miller SE, Al Hinai AS, et al. MBD4 guards against methylation damage and germ line

deficiency predisposes to clonal hematopoiesis and early-onset AML. *Blood*. 2018;132:1526–34.

3. Alekseeva IV, Bakman AS, Iakovlev DA, Kuznetsov NA, Fedorova OS. Comparative analysis of the activity of the polymorphic variants of human uracil-DNA-glycosylases SMUG1 and MBD4. *Mol Biol (Mosk)*. 2021;55:277–88.
4. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17:405–24.
5. Carlson ML, Smadbeck JB, Link MJ, Klee EW, Vasmatzis G, Schimmenti LA. Next generation sequencing of sporadic vestibular schwannoma: necessity of biallelic NF2 inactivation and implications of accessory non-NF2 variants. *Otol Neurotol*. 2018;39:e860–71.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

Received: 17 January 2022 | Accepted: 28 March 2022

DOI: 10.1111/bjh.18194

Donor-transmitted extramedullary acute myeloid leukaemia after living donor kidney transplantation

Here we report a case of donor-transmitted extramedullary acute myeloid leukaemia (AML) through a haploidentical living kidney donation from father to daughter.

Malignancies are one of the most frequent causes of death after solid organ transplantation (SOT). The overall risk is estimated two- to 20-fold greater than in the general population.¹ Immunosuppression represents the main risk factor, depending on the type, its extent and duration. In comparison, transmission of donor-derived cancer is rare and reported in 0.01% to 0.2% of solid organ recipients.^{2,3} The prognosis is poor with a reported mortality of up to 50%.⁴ Acute leukaemia represents a rarity in this regard with only a few case reports published.^{5–13}

A 72-year-old male donated an AB0-compatible and haploidentical kidney to his 44-year-old daughter with a history of end-stage renal disease due to IgA nephropathy. Preoperative donor evaluation did not show any abnormalities in the full blood count nor an elevated uric acid. However, on the day before transplantation a slightly elevated lactate dehydrogenase (LDH) of 315 u/l (normal range: <241 u/l) was observed. Kidney donation and transplantation followed the standard protocol at our institution including induction

immunosuppressive therapy with basiliximab and high-dose steroids, followed by maintenance immunosuppression with tacrolimus, mycophenolic acid and prednisolone. Kidney graft function ensued, and serum creatinine was stable around 2 mg/dl. Graft biopsy 8 days after transplantation did not show rejection nor malignancy.

Six weeks after kidney donation, progressive exhaustion in conjunction with a new-onset thrombocytopenia of $44 \times 10^9/l$ and rising LDH was observed in the donor. Shortly thereafter the patient developed pancytopenia (Table S1). Bone marrow examination led to diagnosis of an adverse risk AML according to the European Leukemia Net classification with a complex karyotype (Table S2).¹⁴ Sequencing of 50 genes frequently mutated in AML by next-generation sequencing (NGS) did not reveal any additional mutation. The patient was enrolled in the CPKC412E2301 trial and received one course of induction chemotherapy with cytarabine and daunorubicin (3 + 7 protocol) in combination with midostaurin/placebo followed by consolidation chemotherapy consisting of intermediate-dose cytarabine with midostaurin/placebo (ClinicalTrials.gov identifier: NCT03512197). Complete remission was attained and a stem

cell transplantation (SCT) from an HLA-matched, unrelated donor was performed. Unfortunately, 34 days after SCT an early recurrence of AML was diagnosed, and the donor died 10 days later due to relapsed AML.

Early after diagnosis of AML in the donor an intensive follow-up regimen of the recipient was established. Allograft nephrectomy was discussed with the recipient but was repeatedly declined. Five months after kidney transplantation the recipient was admitted because of newly occurring severe pain in her lumbar spine, sudden onset left-sided peripheral facial nerve palsy and an ipsilateral hearing loss. Cranial magnetic resonance imaging showed an infiltrative process of the left temporal bone. ^{18}F -fluorodeoxyglucose-positron emission tomography/computed tomography (^{18}F FDG-PET/CT) revealed a strong metabolic activity in the transplanted kidney with diffuse surrounding infiltration and highly FDG-avid lymphadenopathy, peritoneal infiltration, splenomegaly and multiple osteolytic lesions in the vertebrae, pelvic skeleton, proximal femora and both humeri (Figure 1A,B). Bone marrow biopsy and examination of cerebrospinal fluid were unremarkable. Next to infiltration of myeloid blasts (Figure 2), donor origin was confirmed by cytogenetic testing and fluorescence in situ hybridisation revealing a male karyotype in biopsies of the os ilium lesion. Furthermore, as in the donor, no AML-typical mutations could be detected by NGS from osseous biopsy. Genomic profiling by a microarray-based OncoScan CNV Assay (genome-wide detection of copy number changes and copy neutral losses of heterozygosity) of tissue samples from organ donor (from bone marrow biopsy) and recipient (from biopsy of os ilium lesion) reinforced the donor-transmitted origin of the leukaemia (e.g. male sex, identical deletions at 5q34 or 17p13; Figure S1). Immunosuppressive therapy was adjusted to

low-dose tacrolimus and prednisolone. After a first cycle of chemotherapy with cytarabine and daunorubicin ^{18}F FDG-PET/CT showed a reduction of all extramedullary lesions (Figure 1C). After a second cycle of chemotherapy consisting of high-dose cytarabine and mitoxantrone, clinical symptoms improved significantly, and the final PET scan documented a subtotal regression of all extramedullary manifestations. Three months after the initial diagnosis the patient received a SCT from an HLA-mismatched, unrelated donor. Similarly to the course of disease of her father, AML relapsed early 67 days after allogeneic SCT, and was then treated with azacytidine. Unfortunately, the patient died 78 days after SCT due to early recurrence of AML.

The few previously published case reports suggest that donor-derived and donor-transmitted AML tends to occur several years (mean of 28 months) after SOT (Table S3).^{5–13} In six cases extramedullary manifestation was confirmed. In two cases donor origin of AML was assumed because of karyotype of blasts due to different gender of donor and recipient, but detailed genetic analyses were not available. Overall, nine patients achieved complete remission. One patient with complete remission died due to relapse and progression of AML. Of the remaining patients four died due to leukaemia-associated complications and two due to cardiovascular events in complete remission.

Despite small numbers the frequency of extramedullary AML, especially with manifestation in the allograft, seems unusually high. One explanation may be that the transplanted leukaemic stem cells reside in an extramedullary niche within the allograft. Thus, after transplantation leukaemic blasts do not home to the bone marrow, but preferentially stay in extramedullary sites possibly attributable to differential expression of adhesion molecules.

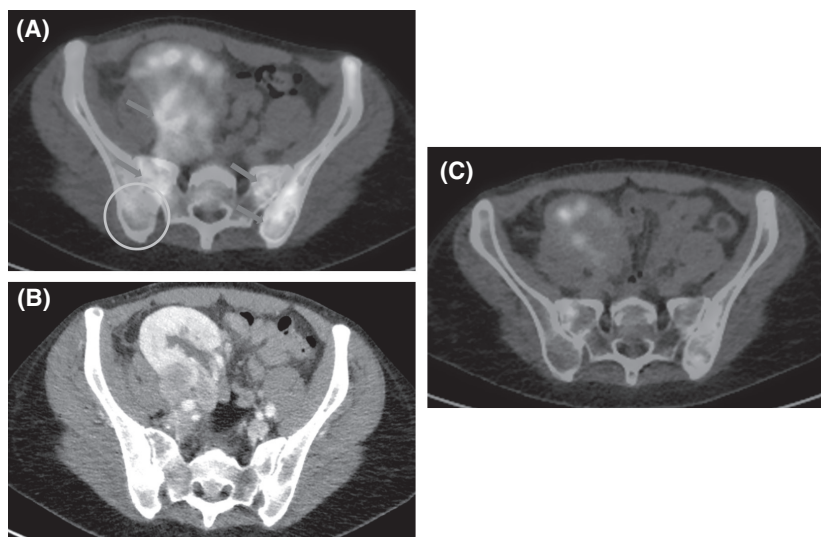


FIGURE 1 ^{18}F -fluorodeoxyglucose-positron emission tomography/computed tomography (^{18}F FDG-PET/CT) scan in the recipient. (A) Initial ^{18}F FDG-PET/CT and correlating contrast-enhanced CT (B) showing diffuse infiltration and enhanced metabolic activity in the transplanted kidney in the right iliac fossa, a diffuse surrounding infiltration, soft tissue proliferation in the right iliac fossa (red arrows) and multiple osteolyses in the vertebra and pelvic skeleton. The green circle indicates osteolysis of the os ilium from which the tissue sample was taken for all further analyses. (C) ^{18}F FDG-PET/CT after second induction therapy displaying a significant regression of metabolic activity in all extramedullary manifestations [Colour figure can be viewed at wileyonlinelibrary.com]

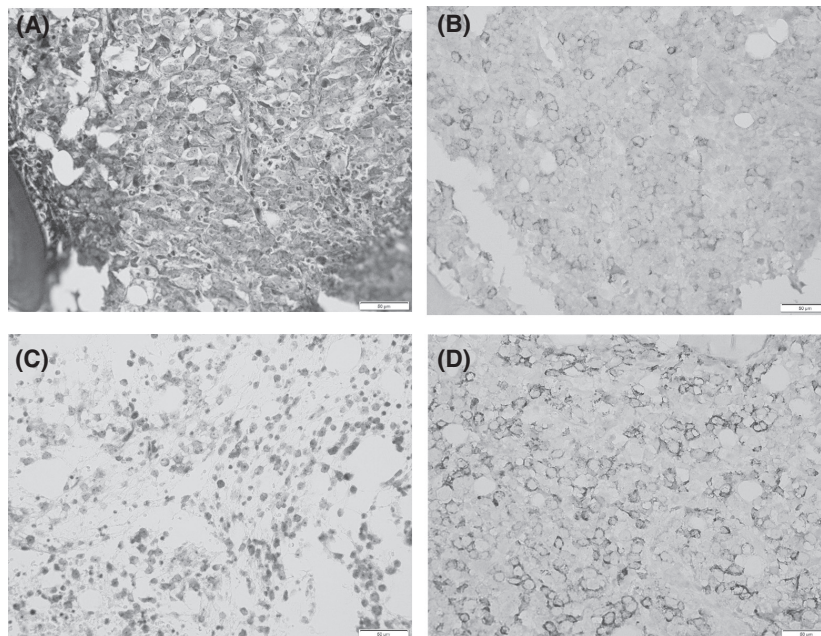


FIGURE 2 Bone marrow biopsies from donor and osseous biopsy (os ilium) from recipient. Sheets of non-maturing pro-erythroblasts with overgrowth of the bone marrow and only small foci of remaining granulopoiesis were seen in trephine biopsies from the donor (A) and the recipient (C). The blast populations in both donor (B) and recipient (D) expressed erythroid lineage markers glycophorin C and transferrin receptor. A and C Giemsa, B and D CD71 immunoperoxidase [Colour figure can be viewed at wileyonlinelibrary.com]

After comprehensive interdisciplinary discussion and review of the literature, we considered several treatment options for our patient including allograft nephrectomy and termination of immunosuppression in order to induce immunological rejection of the AML. Considering that our patient strongly opposed any treatment leading to transplant failure and restart of dialysis, we opted for chemotherapy followed by allogeneic SCT. One reason was, in contrast to previously published case reports, that the AML of our patient was haploidentical as it originated from her father. Accordingly, there were reasonable doubts that immunological effects were potent enough to reject AML. Therefore, the patient was treated with induction chemotherapy followed by SCT from an HLA-mismatched, unrelated donor to allow a graft-versus-leukaemia effect.

In summary, donor-transmitted AML after SOT is extremely rare and prognosis for affected patients remains poor. Donor-transmitted AML may present as widespread myeloid sarcoma without bone marrow infiltration, but involvement of the allograft. Because of its rarity treatment options should include chemotherapy protocols, evaluation of allogeneic SCT, modifying immunosuppressive therapy and considering allograft nephrectomy. Early disease detection in the donor remains challenging because of possibly clinical and laboratory undetectable disease.

ACKNOWLEDGEMENTS

This retrospective data collection was performed in accordance with local legal requirements. Informed consent was

waived by the ethics committee as only anonymous data were published.

The authors would like to thank all nurses, physiotherapists and physicians who have contributed to the care of our patients. This work was supported by the Deutsche Forschungsgemeinschaft (DFG), Collaborative Research Centre (CRC) 1192 (to Tobias B. Huber and Florian Grahammer).

KEYWORDS


acute myeloid leukaemia, donor-transmitted leukaemia, kidney transplantation, myeloid sarcoma, solid organ transplantation


CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Susanne Ghandili and Malte A. Kluger wrote the draft and revised the manuscript. Theo Leitner, Lennart Kirchner, Franziska Modemann, Eike-Gert Achilles, Hans H. Kreipe, Doris Steinemann, Janin Klein, Christine Wolschke, Lutz Fischer, Carsten Bokemeyer drafted the manuscript. Florian Grahammer, Tobias B. Huber, Walter Fiedler, Winfried H. Alsdorf and Maida Mahmud wrote the draft, revised and supervised the manuscript, approved the final version.

Susanne Ghandili¹ 
Malte A. Kluger²
Theo Leitner¹

Florian Grahammer²
 Lennart Kirchner¹
 Franziska Modemann^{1,3}
 Eike-Gert Achilles⁴
 Hans H. Kreipe⁵
 Janin Klein⁶
 Doris Steinemann⁶
 Christine Wolschke¹
 Lutz Fischer⁴
 Carsten Bokemeyer¹
 Walter Fiedler¹
 Tobias B. Huber²
 Winfried H. Alsdorf¹
 Maida Mahmud² 

¹Department of Oncology, Hematology, Bone Marrow Transplantation with Section Pneumology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

²III. Department of Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

³Mildred Scheel Cancer Career Center, University Cancer Center Hamburg, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

⁴Department of Visceral Transplantation, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

⁵Institute of Pathology, Bone Marrow Reference Center, Hannover Medical School, Hanover, Germany

⁶Institute of Human Genetics, Hannover Medical School, Hanover, Germany
 Email: fiedler@uke.de; m.mahmud@uke.de

Susanne Ghandili and Malte A. Kluger contributed equally to this work and share first authorship.

Winfried H. Alsdorf and Maida Mahmud contributed equally to this work and share last authorship.

ORCID

Susanne Ghandili  <https://orcid.org/0000-0001-5655-3155>

Maida Mahmud  <https://orcid.org/0000-0002-1651-8790>

REFERENCES

1. Rama I, Grinyo JM. Malignancy after renal transplantation: the role of immunosuppression. *Nat Rev Nephrol.* 2010;6(9):511–9. <https://doi.org/10.1038/nrneph.2010.102>

2. Engels EA, Pfeiffer RM, Fraumeni JF Jr, Kasiske BL, Israni AK, Snyder JJ, et al. Spectrum of cancer risk among US solid organ transplant recipients. *JAMA.* 2011;306(17):1891–901. <https://doi.org/10.1001/jama.2011.1592>
3. Desai R, Collett D, Watson CJ, Johnson P, Evans T, Neuberger J. Cancer transmission from organ donors-unavoidable but low risk. *Transplantation.* 2012;94(12):1200–7. <https://doi.org/10.1097/TP.0b013e318272df41>
4. Ison MG, Nalesnik MA. An update on donor-derived disease transmission in organ transplantation. *Am J Transplant.* 2011;11(6):1123–30. <https://doi.org/10.1111/j.1600-6143.2011.03493.x>
5. Girsberger S, Wehmeier C, Amico P, Dirnhofer S, Marti E, Halter JP, et al. Donor-derived acute myeloid leukemia in a kidney transplant recipient. *Blood.* 2013;122(2):298–300. <https://doi.org/10.1182/blood-2013-04-497875>
6. Alhurairi A, Chebbo W, El-Gohary G, Chaudhri N, Almohareb F, Ibrahim K, et al. Donor-derived extramedullary acute promyelocytic leukemia post kidney transplant. *Ann Hematol.* 2015;94(3):505–7. <https://doi.org/10.1007/s00277-014-2200-3>
7. Palanisamy A, Persad P, Koty PP, Douglas LL, Stratta RJ, Rogers J, et al. Donor-derived myeloid sarcoma in two kidney transplant recipients from a single donor. *Case Rep Nephrol.* 2015;2015:821346. <https://doi.org/10.1155/2015/821346>
8. Williams T, Aljaitawi OS, Moussa R, McHugh S, Dusing R, Abrahama J, et al. First case of donor transmitted non-leukemic promyelocytic sarcoma. *Leuk Lymphoma.* 2012;53(12):2530–4. <https://doi.org/10.3109/10428194.2012.695360>
9. Kowal M, Hus M, Dmoszynska A, Kocki J, Grzasko N. Acute T cell lymphoblastic leukemia in the recipient of a renal transplant from a donor with malignant lymphoma. *Acta Haematol.* 2008;119(3):187–9. <https://doi.org/10.1159/000137944>
10. Subklewe M, Nagy M, Schoch C, Jenisch S, Siebert R, Gesk S, et al. Extramedullary manifestation of a donor-derived acute myeloid leukemia in a liver transplant patient. *Leukemia.* 2004;18(12):2050–3. <https://doi.org/10.1038/sj.leu.2403498>
11. Bodó I, Peters M, Radich JP, Hess J, Blinder M, Watson MS, et al. Donor-derived acute promyelocytic leukemia in a liver-transplant recipient. *N Engl J Med.* 1999;341(11):807–13. <https://doi.org/10.1056/NEJM199909093411105>
12. Wong RL, Ketcham M, Irwin T, Akilesh S, Zhang TY, Reyes JD, et al. Donor-derived acute promyelocytic leukemia presenting as myeloid sarcoma in a transplanted kidney. *Leukemia.* 2020;34(10):2776–9. <https://doi.org/10.1038/s41375-020-0903-0>
13. Camós M, Esteve J, Rimola A, Grande L, Rozman M, Colomer D, et al. Increased incidence of acute myeloid leukemia after liver transplantation? Description of three new cases and review of the literature. *Transplantation.* 2004;77(2):311–3. <https://doi.org/10.1097/01.TP.0000102549.40531.13>
14. Döhner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Büchner T, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood.* 2017;129(4):424–47. <https://doi.org/10.1182/blood-2016-08-733196>

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.