

Figure 1. Initial bone marrow biopsy, hematoxylin and eosin stain.

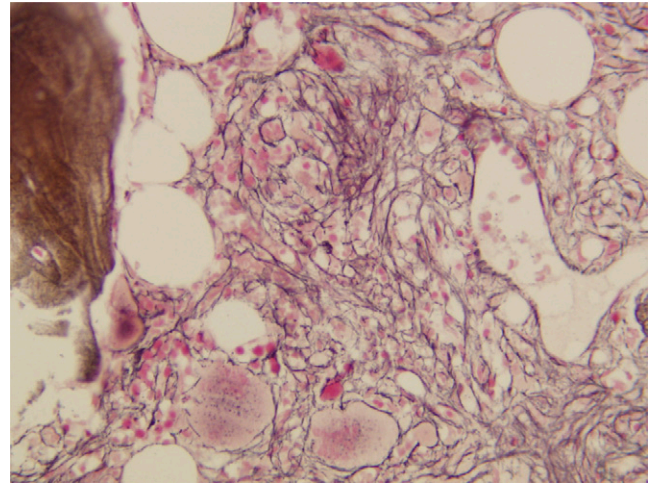


Figure 2. Initial bone marrow biopsy, reticulum stain.

volume was 77 mL/kg, twice the laboratory's top normal range in women (28 mL/kg). Serum erythropoietin level was repeated and was found to have decreased below normal at 3.0 mU/mL. A diagnosis of PV was made, and a therapeutic phlebotomy was initiated.

To date, the patient has undergone 38 therapeutic phlebotomies during a 6-year period, and the patient continues with elevated hemoglobin concentrations and platelet counts. Her symptoms are well controlled, although she continues to have splenomegaly according to both physical examination and radiographic imaging results. She has never had a thrombotic event, nor has she ever received a cytotoxic agent.

Result of a repeated bone marrow biopsy, performed 12 years after the initial diagnosis of PMF and 6 years after the diagnosis of PV, was a markedly hypercellular presence, without reticulum or fibrosis. Genetic study results showed a normal karyotype, and fluorescence in situ hybridization testing results did not reveal abnormalities. A quantitative JAK2 assay result showed an allele burden of 54%. At this point in the course of the disease, there is no evidence of prior MF in this patient.

The case of this patient demonstrates the evolution of transfusion-dependent PMF into phlebotomy-dependent PV, a reversal of the usual progression. According to the DPSS-plus risk system, the patient had 3 adverse features on presentation, placing her in the Intermediate-2 group with a median survival time of 3.6 years. Despite these adverse features on presentation, she has now survived 13 years after the initial presentation and is behaving in an indolent fashion, typical of PV and not PMF.

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To the editor:

Donor-derived acute myeloid leukemia in a kidney transplant recipient

Donor-related malignancy is a rare complication after solid organ transplantation. We present a unique case of a patient with donor-derived acute myeloid leukemia (AML) after kidney transplantation.

A 69-year-old male presented with fatigue, fever, diarrhea, and vomiting. He had a history of polycystic kidney disease and had

received a double deceased kidney transplant from an 81-year-old woman 2 years earlier. The preadmission post-transplant clinical course was uneventful. Current immunosuppression consisted of tacrolimus (3 to 5 mg/day), mycophenolate mofetil (500 mg twice daily) and prednisone (15 mg daily). At presentation, the patient

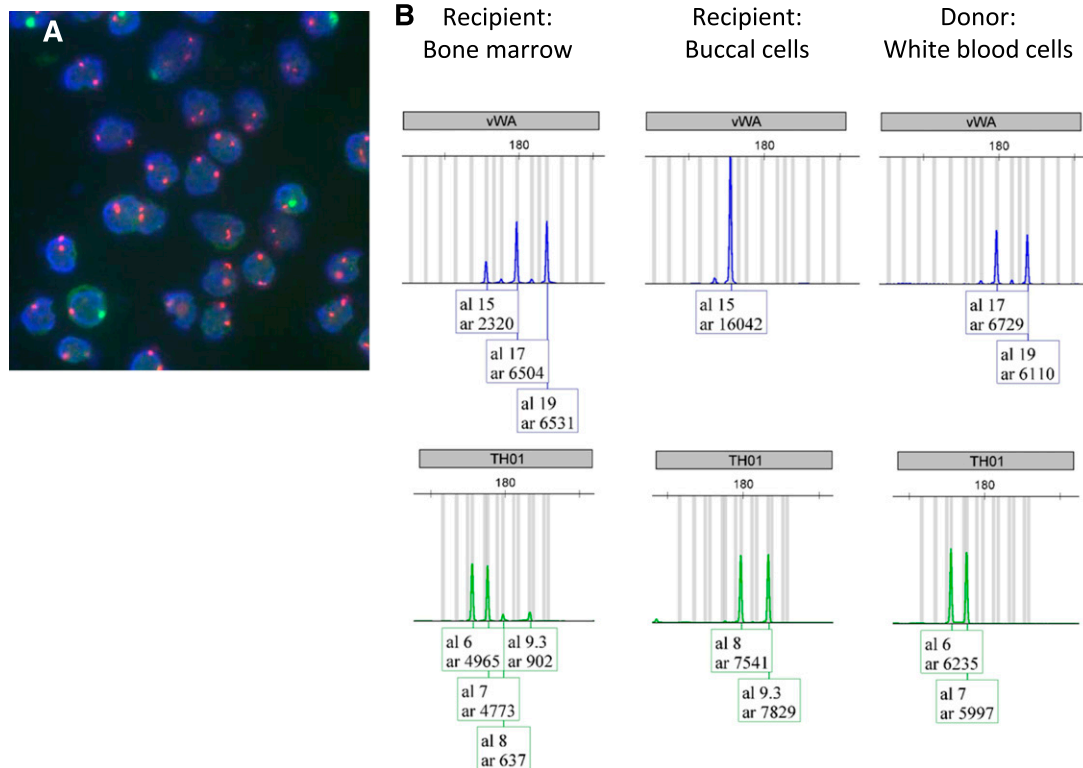


Figure 1. Donor origin of leukemia demonstrated by 2 different molecular methods. (A) Fluorescence in situ hybridization examination of the bone marrow demonstrating 85% of the cells to exhibit a XX chromosomal pattern (2 red signals per nucleus), all of them were morphologic with immature aspect, suggesting the leukemic cells of donor origin. Note the few residual cells of the recipient with XY chromosomal pattern (1 red and 1 green signal per nucleus). FISH was performed using the directly labeled, dual-color (red/green) X- and Y-chromosome probe mix (Xp11.1-q11.1/Yq12) Z-2016 (ZytoVision, Bremerhaven, Germany). The sections were processed with a paraffin pretreatment reagent kit (Abbott/Vysis, Baar, Switzerland), and hybridization was performed according to the manufacturer's specifications. Denaturation was conducted for 10 minutes at 73°C, and the FISH probes were incubated overnight at 37°C in Hybrite (Abbott/Vysis). Counterstaining was performed with 4,6-diamidino-2-phenylindole. The FISH signals were visualized on a Olympus BX43 fluorescence microscope equipped with double bandpass filters for simultaneous visualization of green and red signals. (B) Short tandem repeat profile of the 2 representative chromosomal loci vWA and TH01. Left: Recipient bone marrow cells at diagnosis of AML. Middle: Recipient buccal cells. Right: Donor white blood cells, demonstrating mixed chimerism and donor origin of cells. Taking all 8 discriminative chromosomal loci and the Amelogenin system into calculation, a donor chimerism of 86% can be demonstrated. This is in perfect agreement with the >80% blast infiltration of the marrow and 85% of cells exhibiting an XX chromosomal pattern.

was ill-appearing with aphthous stomatitis and lower limb edema. Laboratory analysis of the peripheral blood revealed pancytopenia without evidence of blasts (supplemental Table 1). Antibiotic treatment (Ceftriaxone) for assumed infectious gastroenteritis was initiated. Eighteen days later, there were 36% of blasts noted on the blood film. Bone marrow trephine biopsy and molecular analysis revealed diffuse infiltration by AML (80% blasts) with mutated nucleophosmin 1. Conventional metaphase cytogenetic analysis showed a normal female karyotype in 17 of 20 metaphases, suggesting donor-derived leukemia. Treatment was initiated according to AMLSG-15-10 (low-dose cytarabine, etoposide, all-trans retinoic acid). Three weeks after diagnosis of AML, the patient died of severe sepsis in aplasia.

Donor origin of the leukemia was confirmed by X chromosome-specific fluorescent in situ hybridization (FISH) of the bone marrow (Figure 1A), and by short tandem repeat analysis of bone marrow and a buccal swab of the patient, as well as of stored leukocytes of the donor (Figure 1B and supplemental Table 2).

The kidney donor had died of intracranial hemorrhage after a head trauma. Medical workup prior to transplantation was unremarkable except for slight normocytic anemia (hemoglobin, 108 g/L) attributed to a knee replacement 1 week earlier. Spleen histology at autopsy was normal and the liver recipient of the same donor is leukemia free at the time of writing.

Kidney transplant recipients have a higher incidence of certain cancers.^{1,2} Almost all of these cancers are recipient in origin. Malignancies of donor origin are extremely rare. Most of them are

donor-transmitted (ie, undetected donor malignancy is present in the transplanted organ). A few cases of donor-derived³ leukemia (ie, normal donor cells that develop into malignancy) have been reported in recipients of liver transplants.^{4,5} In the presented case, 3 disease mechanisms are possible: (1) hematopoietic progenitors that resided in the kidney at the time of transplant engrafted, despite full HLA mismatch, and underwent leukemic transformation; (2) a leukemic stem cell or clone was transplanted via kidney tissue; or (3) an abnormal hematopoietic cell differentiated from kidney tissue (so far, the kidney was considered to be an organ without hematopoietic capacity). Although all 3 hypotheses seem to be extremely unlikely, 1 of them has in fact substantiated in this patient. Due to the long interval between transplant and disease manifestation, the complete absence of signs of a pre-existent malignant hematologic disease of the donor, as well as the fact that the liver recipient of the same donor did not develop leukemia as of yet, we favor the first hypothesis.

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To the editor:

Cerebrospinal leukemoid reaction secondary to VZV meningoencephalitis in an AML patient post allogeneic bone marrow transplantation

Leukemoid reaction (white blood cells [WBCs] $>50\,000/\mu\text{L}$) secondary to inflammatory or neoplastic process describes elevated WBC counts in the peripheral blood (PB).¹ To our knowledge, there has only been 1 case report of a leukemoid reaction in the cerebrospinal fluid (CSF) as a late complication of zoster.² We report a leukemoid reaction in the CSF of an acute myelogenous leukemia (AML) survivor with human herpes zoster (VZV) meningoencephalitis.

A 54-year-old male underwent allogeneic hematopoietic transplantation (AHT) for AML using a fully matched brother. The AML showed diploid cytogenetics; FLT-3, NMP, and CEBPA mutation analysis was not available. His conditioning consisted of melphalan, fludarabine, and alemtuzumab; tacrolimus was used for graft-versus-host disease prophylaxis. He did well post AHT, only having chronic limited skin graft-versus-host disease that did not require continued immunosuppressants. At 1 year post AHT, he received the diphtheria, tetanus, pertussis, meningococcal, pneumococcal, *Haemophilus influenzae* b, hepatitis A and B, and inactivated poliovirus vaccine vaccinations; he was not vaccinated for measles or zoster. He was on bactrim and acyclovir prophylaxis. At 1.8 months post AHT, he presented with headache, seizures, and vesicular skin rash.

Magnetic resonance imaging showed diffuse meningeal enhancement without focal lesions. CSF analysis showed xanthochromic fluid with red blood cells 252/cmm, WBCs 576/cmm, and glucose 159 mg/dL (blood glucose 154).

Two CSF cytology specimens showed monocytic cells that morphologically resembled blasts, with delicate chromatin, moderate gray-blue cytoplasm with vacuoles and azurophilic granules, and occasional mitosis (Figure 1). Corresponding flow cytometry showed 21% and 24% mature monocytes with no immunophenotypic aberrancy. No myeloblasts and no cells of the prior leukemic immunophenotype (CD34+, CD117+, CD33+, CD13+, CD14-) were identified by flow cytometry. There were no nucleated red

blood cells, megakaryocytes, or left-shifted granulocytes in different stages of maturation that would suggest bone marrow

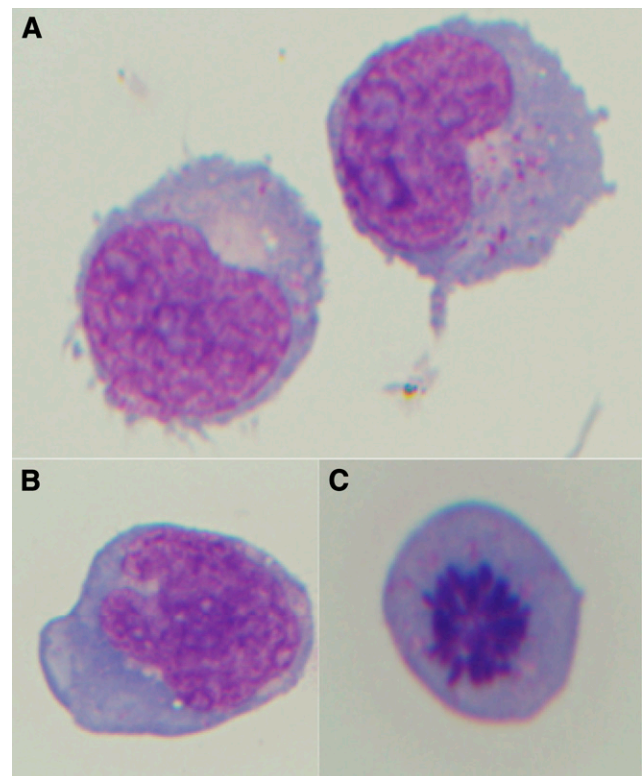


Figure 1. CSF cytology shows atypical reactive monocytic cells. (A) Morphologic features show delicate nuclear chromatin, multiple prominent nucleoli, and moderate gray-blue cytoplasm with azurophilic granules. (B) Some reactive monocytes show delicate lacey chromatin with more irregular nuclear contours. (C) Occasional mitosis is present.