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LETTER TO EDITOR

Successful Bone Marrow Transplantation for XMEN: Hemorrhagic Risk Uncovered

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To the Editor:

XMEN (X-linked immunodeficiency with magnesium defect, Epstein-Barr virus (EBV) infection, and neoplasia) due to MAGT1 mutation is a rare monogenetic disease potentially curable by allogeneic blood or marrow transplantation (BMT) [1]. The published BMT experience in this disease consists of three patients who all experienced early BMT-related mortality that, in retrospect, was associated with significant hemorrhage [2, 3]. We report our BMT experience in three affected males, including two successful outcomes but also a previously unappreciated bleeding diathesis.

All patients with MAGT1 mutation receiving BMT at the National Institutes of Health (NIH) on NCT02579967 were included in the analysis. This protocol was approved by the National Cancer Institute Institutional Review Board; all subjects provided written informed consent. All three recipients were treated per the same BMT platform using reduced-intensity conditioning comprised of pentostatin, low-dose oral cyclophosphamide, and 2 days of pharmacokinetically-dosed busulfan, T cell-replete bone marrow allografts, and graft-versus-host disease (GVHD) prophylaxis with post-transplantation cyclophosphamide, mycophenolate mofetil, and sirolimus. Patients 1 and 3 (P1, P3) received 10/10 human leukocyte antigen (HLA)-matched-unrelated donor allografts, and patient 2 (P2) received an HLA-haploidentical allograft. Patient outcomes related to engraftment, chimerism, EBV control, GVHD, post-BMT complications, and BMT-related mortality were prospectively captured. NKG2D activity in natural killer (NK) and $CD8^+$ T cells was assessed pre- and post-BMT on fresh peripheral blood mononuclear cell samples to support phenotype reversal. Coagulation and platelet function assays were performed in the NIH Department of Laboratory Medicine.

P1, age 29 years (hemizygous *MAGT1* c.712C>T, p.R238X) had a history of EBV-positive lymphoproliferative disorder (EBV-LPD), liposarcoma, persistently elevated blood EBV DNA levels, recurrent sinopulmonary infections with bronchiectasis, hypogammaglobulinemia requiring immunoglobulin replacement therapy, and immune thrombocytopenia, collectively motivating BMT. His bleeding history, in the setting of platelets in the 60–100,000/μL range, included minor, delayed surgical bleeding after his liposarcoma resection; moderate, delayed surgical bleeding after biopsy of his hard palate; one episode of anterior septal epistaxis that required packing; upper gastrointestinal bleeding without identified ulcer; and subarachnoid hemorrhage and epidural/intraorbital hematomas caused by head trauma during a tonic-clonic seizure and requiring multiple platelet transfusions. However, he had also undergone other procedures that did not result in bleeding, such as liver biopsy and necrotizing fasciitis debridement. Two weeks prior to BMT, after placement of a non-tunneled central venous catheter with platelets ranging from 47,000 to 74,000/μL and elevated immature platelet fraction of 21.8% as well as normal prothrombin time (PT) and activated partial thromboplastin time (aPTT), the patient developed significant, delayed bleeding at the catheter insertion site, requiring compression and topical thrombin. Given protracted bleeding after a minor procedure, a thorough pre-BMT coagulation evaluation was performed, revealing no obvious abnormality in platelet or clotting factor function,

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except for slight abnormalities on thromboelastogram (slow rate of clot formation for the activated assay and below normal maximal clot strength for both the activated and unactivated assays), attributed to his mild thrombocytopenia. Normal evaluations included Factor XIII activity, D-dimer, fibrinogen, thrombin time, von Willebrand factor activity and antigen, Factor VIII activity, plasminogen, thrombomodulin, alpha-2-antiplasmin, plasminogen activator inhibitor type 1, and euglobulin lysis test. Post-BMT, the patient experienced significant bleeding related to BK-virus-associated hemorrhagic cystitis from days + 30 through + 43, requiring platelet transfusion and briefly continuous bladder irrigation. At last follow-up 2 years post-BMT, he maintains 100% donor myeloid, T cell, and NK-cell chimerism, blood EBV below the quantification threshold, and normalized platelets, and he has had no sinopulmonary infections off immunoglobulin replacement. Bone marrow biopsies at day + 60 and 1-year post-BMT showed trilineage hematopoiesis and megakaryocytes normal in number and morphology. NKG2D activity, which was low in NK and $CD8^+$ lymphocytes pre-BMT, is akin post-BMT to that of healthy controls (Fig. 1A). Thromboelastogram was repeated 1.5 years post-BMT, and all testing was completely within normal range. The patient has had no subsequent bleeding events since normalization of his platelet count but also has had no significant procedures or challenges to assess his ability to maintain hemostasis.

P2, age 20 years (hemizygous *MAGT1* c.409C>T, p.R137X) had a history of panhypopituitarism secondary to central nervous system EBV-LPD, morbid obesity, autoimmune hemolytic anemia, severe steatohepatitis, recurrent epistaxis requiring emergency room intervention including packing and electrocautery, and hypogammaglobulinemia requiring immunoglobulin replacement. Head MRI pre-BMT revealed no anatomic explanation for epistaxis. Pre-BMT platelet count exceeded 100,000/μL, and PT and aPTT were normal. On day + 16, during post-BMT aplasia, the patient developed massive, posterior epistaxis with hemorrhagic shock requiring intubation, vasopressors, intensive transfusion support, stress-dose steroids, and emergency maxillary artery embolization. He also developed significant BK-virus-associated hemorrhagic cystitis requiring continuous bladder irrigation. Resultant complications included renal failure, delayed neutrophil engraftment, respiratory failure, ventilator-associated pneumonia, bacteremia, and death at day + 44. Bone marrow biopsy on day + 32 showed trilineage hematopoiesis, but hypocellularity with decreased granulocytes and megakaryocytes. At the time of death, he had engrafted with 97% donor myeloid cells. NKG2D activity was demonstrated at day + 28

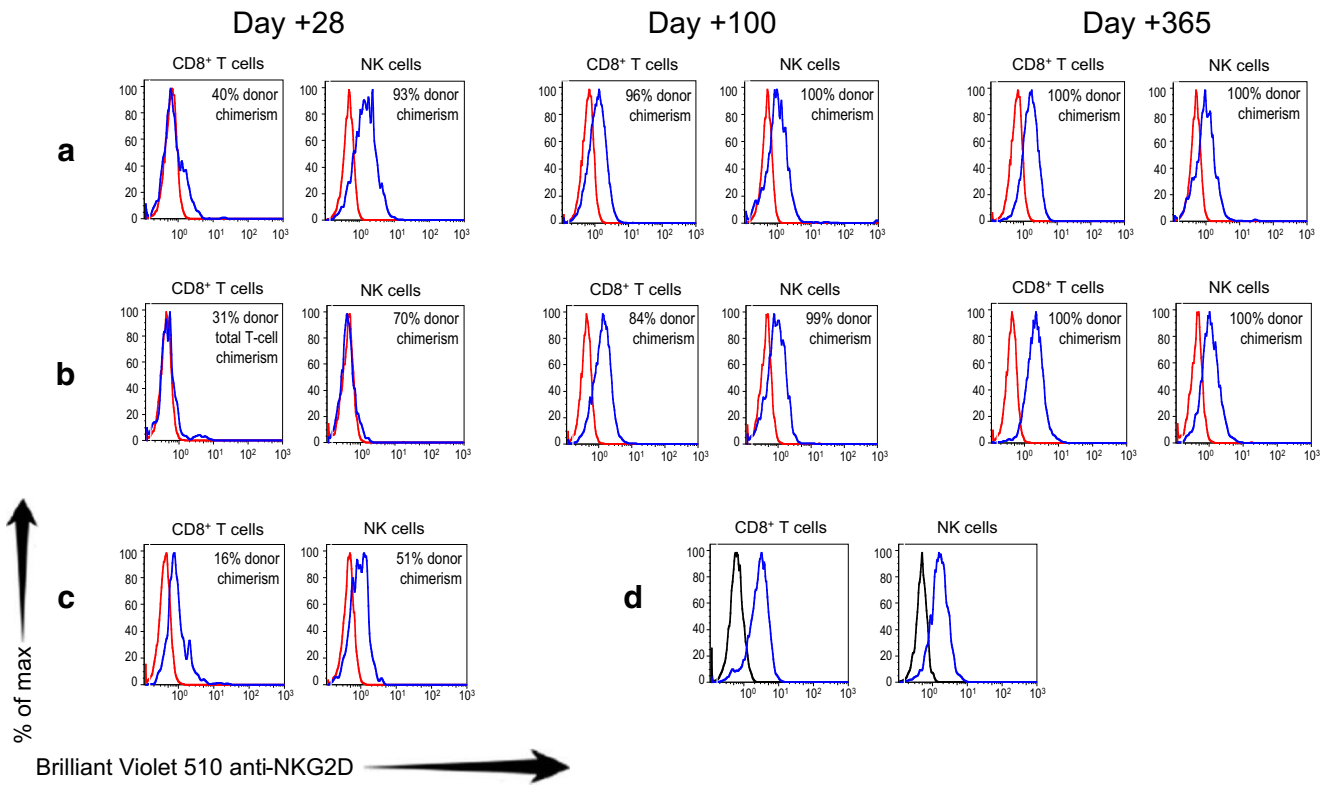

Fig. 1 NKG2D expression by $CD8^+$ T cell and NK subsets increased post-BMT for all patients, in concordance with donor chimerism. Pre-BMT (red) and post-BMT (blue) evaluations are shown for patient 1 (A), patient 3 (B), and patient 2 (C). Lineage-specific donor chimerism performed by the clinical laboratory on flow cytometrically sorted $CD8^+$ T cell and NK-cell subsets drawn on the same day is shown within the plots. (D) Cells from a healthy donor showing the panel containing NKG2D (blue) or a fluorescence-minus-one (FMO) control using the Brilliant Violet 510 isotype (black)

(Fig. 1C). As he remained platelet transfusion-dependent, an extensive coagulopathy evaluation could not be performed.

P3, age 17 years (hemizygous *MAGT1* c.901_902insAA, p.T301KfsX14) underwent BMT following diagnosis of aggressive EBV-LPD treated with two cycles of chemotherapy. His only pre-BMT history to suggest a potential bleeding diathesis was epistaxis of a frequency and severity beyond the range of normal. However, he had never required medical intervention and had undergone peripheral lymph node excision and tooth extractions without bleeding complications. Pre-BMT, platelets were > 100,000/μL, and PT and aPTT were normal. He developed anterior septal epistaxis on day + 15 post-BMT in the setting of platelets of 11,000/μL that resolved with chemical cautery and platelet transfusion, as well as again on day + 16 that resolved just with platelet transfusion. He developed clinically significant BK-virus-associated hemorrhagic cystitis from days + 19 through + 40 post-BMT, requiring platelet transfusion to keep platelets > 30,000/μL. Since allogeneic platelet recovery, he has had no significant bleeding events, including no epistaxis. Bone marrow biopsies at 60 days and 1 year post-BMT showed trilineage hematopoiesis with megakaryocytes normal in numbers and morphology. At last follow-up 1.5 years post-BMT, he has 100% donor myeloid and NK-cell chimerism and 98% donor T cell chimerism, EBV-LPD in complete remission, and freedom from immunoglobulin replacement. NKG2D activity post-BMT has normalized in NK cells and $CD8^+$ T cells (Fig. 1B).

None of the patients developed any acute or chronic graft-versus-host disease.

We report the first two successful BMTs for XMEN, both with follow-up that demonstrates reversal of the disease phenotype and supports BMT as an immunologic cure for this monogenetic disease. Given these results, BMT should be considered for XMEN patients with severe phenotypes. However, since these transplants were performed, an additional XMEN patient underwent BMT at Cincinnati Children's and suffered fatal catastrophic epistaxis, further highlighting the hemorrhagic risk in these patients. In aggregate, the hemorrhagic risk appears significant, and the bleeding events described here and by others are more severe than expected during early, post-BMT thrombocytopenia. The involvement of mucosal sites in many of these pre- and post-BMT bleeding events suggests a platelet problem. Pre-BMT bleeding events were either out of proportion to those expected with the patients' platelet counts or occurred with relatively normal platelet counts, suggesting a qualitative platelet defect that may be unmasked or exacerbated by dense post-BMT aplasia. MAGT1 protein is expressed in platelets, so the defect may be correctable with BMT [4]. However, the precise nature of the seemingly increased bleeding risk has not yet been elucidated and is under active investigation.

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Compliance with Ethical Standards

This protocol was approved by the National Cancer Institute Institutional Review Board; all subjects provided written informed consent.

Conflict of Interest The authors declare that they have no conflict of interest.

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