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### Case Report

# Transmission of lupus anticoagulant by allogeneic stem cell transplantation



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#### ABSTRACT

Passive transmission of autoimmune diseases by allogeneic stem cell transplantation is rare and is ascribed to passive transfer of memory B-cells from donor to recipient. We hereby report a case of transmission of an asymptomatic lupus anticoagulant from a sibling donor to a recipient of transplantation for secondary acute myeloid leukemia. On pre-harvest evaluation, the sibling donor with no history of bleeding or thrombosis was found to have a lupus anticoagulant. After engraftment, the recipient was found to have a new prolonged activated partial thromboplastin time and was subsequently shown to have a lupus anticoagulant on Day +73 after stem cell transplantation. The recipient remained well with no evidence of bleeding, thrombosis, or graft-versus-host disease and was on a stable dose of tacrolimus at the time the lupus anticoagulant was detected. There was no other identifiable trigger for the appearance of a lupus anticoagulant.

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## Introduction

Allogeneic stem cell transplantation (SCT) is a potentially curative procedure for patients with hematological malignancies. Bone marrow and peripheral blood stem cells from related and unrelated donors are subject to a comprehensive evaluation to prevent the transmission of communicable diseases.<sup>1,2</sup> Few cases illustrating the transmission of autoimmune disease by SCT have been reported in the literature.

Such phenomena were attributed to the transmission of donor lymphocytes with SCT. The lupus anticoagulants (LAC) are heterogeneous antibodies that bind to a complex of anionic phospholipids that bind to one or more blood coagulation proteins to influence their contribution in coagulant-based assays.<sup>3</sup> To our knowledge, there had not been any previously reported cases of the asymptomatic transmission of LAC by SCT. We hereby report a case of transmission of a LAC from a sibling donor to a recipient by SCT.

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## Case report

A 63-year-old Caucasian male, with no significant past medical history, was initially diagnosed with myelodysplastic syndrome with French, American and British (FAB) classification of refractory anemia with excess blasts; with complex cytogenetics and a revised international prognostic scoring system (IPSS-R) of 8.5.<sup>4</sup> A bone marrow biopsy showed 6% blasts at the time of diagnosis. The patient received two cycles of azacitidine (75 mg/m<sup>2</sup> for seven doses). A repeat bone marrow biopsy showed transformation to secondary acute myeloid leukemia (AML) FAB subtype M6. The patient received induction chemotherapy with cytarabine (100 mg/m<sup>2</sup> for seven doses) and idarubicin (12 mg/m<sup>2</sup> for three doses) and achieved minimal residual disease with a markedly hypocellular marrow and no residual blasts. Given the high risk nature of his disease, the patient proceeded to allogeneic peripheral blood stem cell transplantation from his human leukocyte antigen (HLA) and ABO-identical brother. The transplant conditioning regimen included fludarabine (daily dose of 30 mg/m<sup>2</sup> on Days -5 to -2) and melphalan (140 mg/m<sup>2</sup> on Day -2). Immunosuppression consisted of tacrolimus and methotrexate (10 mg/m<sup>2</sup> on Days +1, +3, +6, +11). Post-transplant course was complicated with *Klebsiella pneumoniae* and vancomycin resistant enterococci bacteremia. The patient engrafted white cells on Day +15. On Day +73 the patient was doing well without evidence of graft-versus-host disease (GVHD), thrombosis, or bleeding. He had an isolated prolongation of activated partial thromboplastin time (aPTT) of 56 s (normal range: 23-35). The patient's baseline value for aPTT prior to transplantation was 31 s. The prothrombin time (PT) was 12.9 s (normal range: 9.3-12.8). The thrombin time was normal excluding heparin contamination. Mixing studies failed to correct the prolonged aPTT. Dilute Russell Viper venom time (DRVVT) was 109.7 s (normal range: <55.1 s). DRVVT confirmatory test was 47.2 s with a ratio of 2.2 (normal range: <1.3) demonstrating strong serologic evidence of a lupus anticoagulant (LAC). Serologic testing for anticardiolipin antibodies (IgG, IgM, IgA) and  $\beta$ 2 glycoprotein I antibodies (IgG, IgM, IgA) was negative. The elevated PTT persisted. The patient's sibling donor was found to have a prolonged aPTT of 56 s prior to donation. The screening test for DRVVT was 125.9; the confirmatory test was 41.7 with a ratio of 2.8 also indicating strong serologic evidence of LAC. These findings suggest the transmission of LAC from sibling donor to recipient.

## Discussion

Autoimmune syndromes and autoantibodies are suspected to develop after autologous and allogeneic SCT. In a retrospective analysis of 1292 patients of post-transplantation (465 autologous and 827 allogeneic), 3% of patients developed a *de novo* LAC.<sup>5</sup> The development of LAC in this analysis was related to the use of cyclosporine A, use of T-cell depletion for GVHD prophylaxis, use of a busulfan and cyclophosphamide (BUCY) regimen, and reactivation of cytomegalovirus (CMV) or other herpes viruses.<sup>5</sup> Autoantibody production after SCT has been ascribed to *de novo* antibody production from naive

B-cells or passive transfer of memory B-cells from the donor.<sup>6,7</sup> B-cell functional recovery after SCT is slow and incomplete often resulting in seronegativity to previous immunizations; regardless of the immune status of the donor.<sup>8</sup> Tracking of transferred B-cell clones showed that production of antigen-specific plasma cells from donor memory B-cell pool requires further exposure to antigen yet results in the production of antibodies with identical affinity to those produced in the donor.<sup>9</sup>

Antiphospholipid antibodies (aPL) are autoantibodies directed against phospholipid binding proteins that most commonly are  $\beta$ 2-glycoprotein I, cardiolipin, and many blood coagulation proteins. LACs are aPL that interact with blood coagulation proteins and influence clot-based blood coagulation protein assays. The presence of lupus anticoagulants in healthy individuals has been estimated to be 1.0-5.6% while in individuals with systemic lupus erythematosus (SLE) it is much higher; 11-86%.<sup>10</sup> The presence of LACs, in the absence of any history of bleeding or thrombosis, is frequently discovered by routine aPTT screening performed prior to an elective surgical procedure. The diagnosis of antiphospholipid syndrome (APLS) requires evidence of arterial or venous thrombosis or pregnancy morbidity associated with the detection of aPL antibodies on two separate occasions at least 12 weeks apart.<sup>3,10</sup> In healthy individuals without SLE, the clinical significance of persistent asymptomatic aPL remains uncertain and the risk of development of thrombosis is unknown.<sup>10</sup> APLS occurrence after SCT has been reported before but only in the context of acute/chronic GVHD and associated with cerebral thrombosis and catastrophic APLS.<sup>11-15</sup>

Ritchie et al.<sup>13</sup> described a case of the transmission of APLS from a sibling donor with known SLE, APLS, and history of thrombosis where the recipient developed symptomatic APLS with cerebral thrombosis and also a high titer anticardiolipin and anti-ds-DNA antibodies (identical to donor). In that report, aPL positivity was predated by the onset of chronic GVHD six months after SCT suggesting that memory B-cell activation occurred as the result of the presentation of phospholipid antigens from epithelial tissue induced by GVHD. In our case, we had prior knowledge that the sibling donor had LAC, yet we decided to proceed with SCT as we believed that the benefit in proceeding to SCT quickly, as the patient had a high risk for AML relapse, outweighed the theoretical risk of the development of symptomatic APLS. We cannot exclude the possibility of the development of a *de novo* autoimmune LAC in the recipient, independent of the transmission of donor lymphocytes capable of producing aPL (including LAC). Cell membrane damage, related to the toxicity from the conditioning regimen, may expose antigens, such as the hexagonal phase lipids, that are not otherwise present in the intact cell membrane. Such lipid could serve as an epitope for the development of LAC or other aPL as a *de novo* phenomenon.<sup>16</sup> We believe that this possibility is less likely in the current case as the patient received a reduced-intensity conditioning regimen, had no evidence of GVHD, and was on a stable dose of tacrolimus at the time of the detection of the LAC. Our observations suggest the passive transfer of donor B-cells capable of producing a LAC. The antigen trigger for development of the LAC in our case remains obscure and may be related to infectious complications occurring in the peri-transplant period.

## Conflicts of interest

The authors declare no conflicts of interest.

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