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Transformed large B-cell lymphoma in rituximab-allergic patient with chronic lymphocytic leukemia after allogeneic stem cell transplant: successful treatment with ofatumumab

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Transformation of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) to a more aggressive lymphoma, including large B-cell (LBCL) or Hodgkin disease, is a well-recognized complication termed Richter transformation (RT) [1]. Its occurrence following allogeneic hematopoietic stem cell transplant (alloHCT) is extremely rare, with only one patient having been reported to date [2]. This patient was treated successfully with withdrawal of immunosuppressive drugs and donor lymphocyte infusion (DLI). Here, we present a case of RT following alloHCT in a 43-year-old female with a history of severe anaphylactic reaction to rituximab, a drug commonly used in patients with relapse or post-transplant lymphoproliferative disorder (PTLD) [3–5]. The patient was successfully treated with withdrawal of immunosuppressive drugs and ofatumumab, a fully human anti-CD20 monoclonal antibody with high efficacy in CLL and indolent lymphomas [6,7]. To our knowledge, ofatumumab has not been reported in either a post-transplant or LBCL setting.

In 1998, a 43-year-old female was diagnosed with CLL/SLL by lymph node (LN) and bone marrow (BM) biopsies. Cytogenetics revealed a 14q32 deletion in three out of 17 metaphases. She was followed for 1 year without therapeutic intervention. In October 1999, she developed symptomatic lymphadenopathy and was treated with fludarabine and prednisone for 6 months. Rituximab could not be given for more than two cycles due to severe anaphylactic reactions. Starting in 2003, she intermittently received multiple chemotherapies, including fludarabine, cyclophosphamide, vincristine, steroids and most recently bendamustine. Given the short duration of responses, emerging cytogenetic

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aberrations (trisomy 12) and recurrent infections (primarily in the lung and sinuses), the patient was referred for consideration of alloHCT in April 2011.

Prior to transplant, her BM had a prominent diffuse, interstitial lymphoid infiltrate comprising 80–90% cellularity [Figure 1(A)]. The cells were small to intermediate in size with scant cytoplasm on hematoxylin and eosin (H&E) staining [Figure 1(B)], and had the usual characteristics of CLL/SLL, including scant cytoplasm and clumped chromatin, on Wright–Giemsa staining [Figure 1(C)]. Flow cytometry demonstrated a lambda-monotypic B-cell population that expressed CD5, dim to absent CD20 and uniform CD23, without CD79b, further supporting a diagnosis of CLL/SLL. Cytogenetics confirmed the persistence of del 14 and trisomy 12.

In May 2011, she underwent human leukocyte antigen (HLA) fully matched sibling alloHCT following non-myeloablative conditioning (fludarabine, cyclophosphamide and low-dose total body irradiation) for CLL. Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine and mycophenolate mofetil (MMF). Neutrophil and platelet engraftment occurred within 2 weeks after alloHCT. The first 30 days post-transplant was complicated by cytomegalovirus (CMV) pneumonitis, *Pseudomonas aeruginosa* sepsis and BK virus-induced hemorrhagic cystitis. She was treated successfully for all complications. Two months after alloHCT, she developed grade III acute GVHD, involving the skin and gastrointestinal tract (GIT). High-dose steroids and MMF were added to cyclosporine. Three months after alloHCT, she was diagnosed with nocardiosis (*Nocardia asteroides*) and invasive fungal infection (non-sporulating saprophytic fungus) in the lung. These infections were treated accordingly.

While the patient had numerous infections and GVHD exacerbations, her CLL responded very well to alloHCT. Post-transplant restaging positron emission tomography (PET)/computed tomography (CT) scans demonstrated a remarkable and progressive decrease in both the size and standardized uptake value (SUV). CLL/SLL cells in the BM decreased from 80 to 20% in the first month and to 5% in the third month. At 6 months, when the patient was taking cyclosporine only and clinically doing well (no fevers, night sweats or fatigue), a routine BM biopsy contained neoplastic cells. In comparison to prior biopsies, however, the cells were large, with vesicular chromatin and prominent nucleoli, expressing the B-cell markers CD20 and PAX-5 [Figure 2(A)]. They had partial CD30 expression and were predominantly CD45 positive, without CD15 or Epstein–Barr virus encoded RNA (EBER) as determined by *in situ* hybridization. The morphologic and immunohistochemical features were diagnostic of LBCL involving the marrow. Flow cytometry identified a 0.1% lambda-monotypic B-cell population that had CD5, dim CD20 and CD23 [Figure 2(B)]. The average forward scatter of this small population was increased [Figure 2(B)] compared to prior studies, indicating increased cell size. Molecular testing to look for B-cell receptor gene rearrangements demonstrated a clonal B-cell population [Figure 2(C)], and a major peak at 127 base pairs was clonotypic to that previously described in this patient's prior aspirates containing her CLL/SLL cells. Thus, immunophenotypic and molecular data support the view that this LBCL represents a RT of the patient's previously described CLL/SLL. Fluorescence *in situ* hybridization (FISH) of the BM using probes to ETV6 (12p13), RUNX1 (21q22), LSI D13S319 (13q14.3) and LAMP1 (13q34) showed that 0.1% of 1000

interphase cells examined had a signal pattern consistent with the presence of trisomy 12. This rate was within normal control limits (0–0.13%) for our laboratory. Thus, no evidence was found of chronic lymphocytic leukemia, characterized in previous studies by abnormalities including trisomy 12. PET/CT scans showed no evidence of lymphoma. Epstein–Barr virus (EBV) was negative in marrow and blood studies as determined by polymerase chain reaction (PCR).

Treatment of LBCL included withdrawal of cyclosporine and administration of ofatumumab (300 mg IV initially and then 2000 mg IV weekly for seven doses). The first dose was given in an inpatient setting because of her history of rituximab-induced anaphylaxis; however, all doses were well tolerated. Cyclosporine withdrawal induced reactivation of GIT GVHD and required higher doses of steroids. A BM aspiration-biopsy repeated after eight doses of ofatumumab showed no evidence of CLL/SLL or LBCL. Because of the reintroduction of steroids and resumption of cyclosporine, ofatumumab maintenance was started (2000 mg IV months for four doses). After 11 doses of ofatumumab (5 months after treatment), she still had no evidence of lymphoma as determined by subsequent imagings and BM biopsies (the patient had bone marrow biopsies at 2 and 4 months after her presentation of large B-cell lymphoma, and both were negative for either large B-cell lymphoma or CLL/SLL by morphology and ancillary testing: flow cytometry, FISH, cytogenetics and B-cell clonality studies by PCR).

Allergic reactions to ofatumumab have been reported previously [8], particularly during the first infusion; however, ofatumumab has been successfully administered in a patient with severe rituximab allergy [9]. This is consistent with our case. In addition to ofatumumab's favorable safety profile, our case suggests that ofatumumab, along with withdrawal of immunosuppression, was effective in LBCL. Although it is still a short time after treatment, given the fact that she has no evidence of this aggressive lymphoma, treatment is considered to be effective. The current attainment of complete response with ofatumumab is encouraging, and provides a reportable experience with this new agent in a post-allotransplant setting.

Our case also demonstrates an important point for leukemia and transplant physicians: the timing of referral for alloHCT in patients with CLL. AlloHCT is highly effective in CLL, and is associated with 4-year survival rates of 60–70% [10]. However, our case was only considered for alloHCT as a “last resort” after failing multiple chemotherapy regimens. By this time, she had significant sino-respiratory infections with low performance status and BM reserve. Although infectious complications diagnosed after alloHCT were successfully treated, it is worth considering alloHCT while the patient is still relatively healthy.

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Figure 1.

Pre-transplant bone marrow sampling. (A, B) H&E stained sections of the trephine biopsy at (A) $\times 10$ and (B) $\times 100$ oil. (C) Wright–Giemsa stained bone marrow particle crush at $\times 100$ oil. (D) Flow cytometry of bone marrow aspirate samples. The majority of cells did not have increased forward scatter. The clone expressed uniform CD5, dim to absent CD20, CD23 and lambda light chain, but did not express CD79b.

Figure 2.

Post-transplant bone marrow sampling documenting Richter transformation. (A) Neoplastic cells exhibited prominent nucleoli and vesicular chromatin. They expressed CD20 and PAX-5. Images were all captured with a $\times 100$ oil objective. Main panel on left represents H&E stained core biopsy. Insert photo on left demonstrates large (3–4 times diameter of adjacent red cells) neoplastic lymphocytes, one with a prominent nucleolus, seen on Wright–Giemsa stained marrow smear. (B) The B-cell clone had increased forward scatter as determined by flow cytometry, but had the same expression of CD5, CD20, CD23 and lambda light chain as previously characterized (clonal population highlighted by red circle). Forward scatter plot demonstrates back-gated cells corresponding to the population within the red circle. (C) B-cell clonality assay by PCR (using Framework 2 and 3 primer sets) showed clonal rearrangement of the immunoglobulin heavy chain gene (IgH) in the bone marrow aspirate sample.