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To the editor:

Transmission of leukemic donor cells by allogeneic stem cell transplantation in a context of familial CLL: should we screen donors for MBL?

A family history of chronic lymphocytic leukemia (CLL) is one of the best characterized risk factors for the development of CLL. First-degree relatives of individuals with CLL have a 3- to 8-fold increased risk for CLL.^{1,2} CLL often has an indolent behavior, but some patients show an aggressive course, are resistant to purine analogs and therefore are eligible for allogeneic stem cell transplantation (ASCT).³

We report here the case of a 45-year-old man who was referred in 1997 for CLL with lymphocytosis ($30 \times 10^9/L$) and lymphadenopathies. Immunophenotyping studies on blood cells revealed monoclonal B lymphocytes (Matutes Score 5), and a κ immunoglobulin light chain restriction. Because of a quick relapse after fludarabine treatment and the existence of a HLA matched brother, the patient underwent a peripheral blood stem cell transplantation with myeloablative conditioning in March 2001. A limited chronic graft-versus-host disease (GVHD) was observed and the patient received cyclosporine for 2 years. Finally, complete remission and full donor chimerism were obtained.

In March 2006, the 63-year-old donor brother was referred for lymphocytosis ($35 \times 10^9/L$) evolving over a period of 2 years. Immunophenotyping of blood cells revealed a monoclonal B-cell population expressing λ immunoglobulin light chain restriction (Matutes Score 5). In October 2006, the recipient brother presented with lymphadenopathies and a discrete lymphocytosis ($5.5 \times 10^9/L$). Flow cytometric analysis identified a monoclonal B-cell population expressing λ immunoglobulin light chain.

Both brothers exhibited normal karyotypes, but FISH analysis showed a monoallelic deletion at 13q14. PCR amplification of IGHV-D-J rearrangements with FR1 primers demonstrated a monoallelic, unmutated VH1 (IGHV 4-69*01) rearrangement in the initial B-CLL clone in the recipient before PMST.⁴ After allograft, this patient showed a new unmutated, biallelic VDJ rearrangement (VH1 4-69*01 + VH4-34*01). An identical biallelic rearrangement was detected in the donor CLL (Figure 1). Further PCR amplification and sequencing retrospectively confirmed the presence of this biallelic IGHV-D-J rearrangement in the donor blood before ASCT, while WBC was normal (Figure 1).

Monoclonal B-cell lymphocytosis (MBL) is an asymptomatic hematologic condition characterized by lymphocytosis $< 5 \times 10^9/L$ and a CLL-like phenotype.⁵ Here we report the second case of transmission of CLL by ASCT, linked to the presence of MBL in the graft. In our observation, CLL developed as an aggressive form in both brothers, whereas Perz described indolent CLL in the recipient and persistence of MBL in the donor. Of note, the latter case showed a somatically mutated VH4-34 rearrangement whereas in the present cases, VH genes were unmutated.⁶ Taken together, this suggests that genetic microenvironment and immune system do not influence CLL course.

These observations raise the question of identifying occult malignancies in transplant donors, specifically for CLL.⁷ Indeed, MBL is more

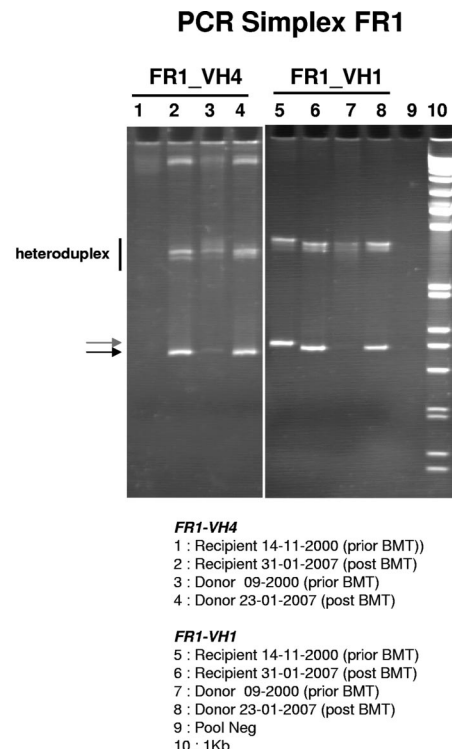


Figure 1. PCR analysis of IGHV-D-J rearrangements using FR1 Biomed-2 primers. Samples as indicated. Arrows indicate clonal rearrangements. Vertical black bar indicates the position of heteroduplexes.

frequent in sibling transplant donors to CLL patients (15.4%) than in the general population (3%), and MBL prevalence increases with age in first-degree relatives of patients with sporadic CLL.^{8,9}

In conclusion, we propose the use of sensitive methods for the systematic screening of blood donors for the presence of MBL, particularly when a history of CLL is known in the family.^{10,11}

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