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Identical IGHV-D-J gene rearrangement may precede the clinical onset of chronic lymphocytic leukemia by several years

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Abstract

The pathogenesis of chronic lymphocytic leukemia (CLL) has not been fully elucidated. Moreover, the time required for the initial B lymphocyte IGH gene rearranged clone to manifest as a clinical entity remains unknown. We searched for previous IGH gene rearranged B lymphocyte clones in healthy people who developed CLL and estimated the time for the clone to become clinically detectable. To this aim, we identified all incident cases of CLL diagnosed in a cohort of 15,055 healthy subjects aged 18-65 years enrolled in a prospective survey on thrombophilia. Seven CLL cases were identified at a median follow-up of 54 months (range, 18-89). The estimated incidence was 0.46 cases/10,000 person-years (CI: 0.17-1.00). A PCR was performed to detect IGH gene rearrangement at enrollment and at CLL diagnosis. Comparison was possible in six subjects. In five, the same IGH gene rearrangement and gene sequence were already present 39-89 months before CLL diagnosis. A mutated status was identified in four of five cases. The median age at diagnosis was 66.2 years, and all subjects were asymptomatic. Two patients expressing the IGHV1-69 gene with an unmutated status required treatment 16 and 40 months after diagnosis. The IGHV4 family genes were rearranged in the remaining cases, all showing a mutated status. No additional rearrangements or mutations in the rearranged gene were found during follow-up. An identical clonal IGH gene rearrangement may precede CLL diagnosis by several years.