To the editor:

Rearrangement of NOTCH1 or BCL3 can independently trigger progression of CLL

Recent data indicate that NOTCH1 mutations significantly increase the risk of CLL progression toward Richter syndrome (RS) and chemoresistance,1,2 and that activation of NOTCH1 at time of CLL diagnosis is an independent prognostic factor of poor survival.1,3 We report here a case of CLL with a novel rearrangement of NOTCH1 identified at the time of RS. The patient, a 58-year-old male, was diagnosed with CLL (unmutated VH) in RS in June 2003. Cytogenetic analysis and FISH on peripheral blood (PBL), bone marrow (BM), and lymph node (LN) cells showed 2 related clones: one with an isolated +12 and a second with +12 and dic(9;14)(q34;q32) (supplemental Table 1, available on the Blood Web site; see the Supplemental Materials link at the top of the online article). FISH analysis of dic(9;14)(q34;q32) indicated that this aberration resulted in juxtaposition of 3'IGH and 5'NOTCH1, as evidenced by the loss of sequences telomeric to the breakpoints (Figure 1A-D). These imbalances were confirmed by array CGH (data not shown). The targeting of NOTCH1 by dic(9;14) was evidenced by qRT-PCR analysis, which showed a 10-fold up-regulation of NOTCH1 mRNA (Figure 1E) and a low expression of the neighboring genes (GPM11, CARD9, DNL2). Immunoblotting of a cell lysate from LN with a NOTCH1 antibody recognizing active, cleaved NOTCH1 (Val1744) identified a band corresponding to activated intracellular NOTCH1 (Figure 1F), suggesting an additional truncating mutation. Indeed, sequence analysis identified a CT7544–7545/P2515fs. Despite treatment, 2 clones harboring CT7544–7545/P2515fs, in the nucleus, but lacking TP53, showed a complex karyotypic pattern, including dic(9;14) and 5'IGH-BCL3 allele is recurrent in T-ALL4 and CLL.1,3,5

The patient was treated and achieved complete remission (supplemental Table 1). In 2007, however, CLL relapsed and an examination of BM identified a clone with a sole dic(9;14) disruption frequency associated with RS6 was not observed in the analyzed

References

Four months later, the patient developed peripheral T-cell lymphoma, a rare recurrent event in CLL. Altogether, the present case allows us to deduce the sequence of multiple genetic defects driving development and progression of CLL. An initial clone with 12, likely present at a presymptomatic CLL phase, later acquired an activating mutation of NOTCH1. Subsequent acquisition of dic(9;14)/IGH-NOTCH1 triggered Richter transformation. After a few years, a persistent, chemorefractory mutated clone underwent another hit, t(14;19)/IGH-BCL3, which initiated the second progression that was followed by a fatal CLL-unrelated T-cell lymphoma. Our findings confirm the risk of activating mutations of NOTCH1 in Richter transformation of CLL, particularly CLL with 12, and highlight that a residual chemotherapy-
resistant NOTCH1-mutated clone is at risk of acquiring further progression-associated hits. Besides the known t(14;19)(q32; q13)/IGH-BCL3,8-10 we also identified dic(9;14)(q34;q32)/IGH-
NOTCH1, which so far has not been reported in B-cell leukemia/lymphoma, as a novel genomic aberration capable of triggering RS.

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References


To the editor:

Persistently high quality of life conferred by coexisting congenital deficiency of terminal complement C9 in a paroxysmal nocturnal hemoglobinuria patient

Paroxysmal nocturnal hemoglobinuria (PNH) clone bears a PIGA mutation and fails to express glycosylphosphatidylinositol-linked membrane proteins such as complement-regulatory CD55 and CD59, leading to complement-mediated intravascular hemolysis and thrombosis. The advent of eculizumab, an inhibitor of terminal complement C5, provides good quality of life (QOL) by preventing hemolysis and thrombosis,1,2 and may improve prognosis of PNH patients.3 However, the safety of its long-term use for more than 10 years1,2 and the pathogenesis of eculizumab-associated extravascular hemolysis have not been established.4 For the hemolysis, steroid, splenectomy,5 and C3-targeted therapy6 have been proposed, despite their individual risks.7 In 1980, we found a PNH patient with a coexisting congenital deficiency of C9, still the only case globally.8 Presently, the patient is 78 years old and has kept a high QOL (no experience of massive hemolysis, thrombotic events, critical infection, or malignant diseases) for more than 31 years after the PNH diagnosis. Of note, the patient manifests very low levels of PNH hemolysis (Figure 1A-B) and marrow failure (Figure 1A). The high QOL may reflect that the C9-deficiency prevents membrane attack complex (C5b-9) formation but allows immune reactions by generation of C5a and C5b-8.7 Currently, virtually all erythrocytes (and granulocytes) of the patient showed the PNH phenotype (Figure 1A-C). Whole blood cells had the same PIGA mutation in 1998 and 2011 (Figure 1D), indicating that the cells are of a single PNH clone. Marrow cells showed a normal karyotype. These findings support the concept that clonal hematopoiesis in PNH is a benign process. The clinical features suggest the safety and efficacy of long-term inhibition of terminal complement including C9 for even elderly PNH patients. Thus, we propose that C9 targeting is another option for PNH therapy.5

Hemosiderinuria (Figure 1E) is an indicator of intravascular hemolysis, probably induced by C5b-8 in the C9-deficient patient.7
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