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.

The online version of this article contains a data supplement.

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**Contribution:** K.D.K. and I.W. designed and performed the research, analyzed data, and wrote and approved the manuscript; L.M. analyzed data and wrote and approved the manuscript; A.B. and C.G. treated the patient, contributed vital patient information, and approved the manuscript; J.F.F. performed array CGH, analyzed data, and approved the manuscript; P.V. analyzed data and wrote and approved the manuscript; and J.C. designed the research, analyzed data, and wrote and approved the manuscript.

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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 membrane attack complex (C5b-9) formation but allows immune-mediated clearance,8 probably induced by C5b-9 in the C9-deficient patient.9,10 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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**Contribution:** K.D.K. and I.W. designed and performed the research, analyzed data, and wrote and approved the manuscript; L.M. analyzed data and wrote and approved the manuscript; A.B. and C.G. treated the patient, contributed vital patient information, and approved the manuscript; J.F.F. performed array CGH, analyzed data, and approved the manuscript; P.V. analyzed data and wrote and approved the manuscript; and J.C. designed the research, analyzed data, and wrote and approved the manuscript.

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**References**


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Surprisingly, the patient had C3d-bound erythrocytes (Figure 1C) that often appear in PNH patients on eculizumab and are susceptible to extravascular hemolysis. Thus, the patient manifests extremely low levels of both intra- and extravascular hemolysis. It is interesting to verify whether ordinary PNH patients harbor dormant extravascular hemolysis. Judging from the fluorescence intensity of C3d-positive erythrocytes, the amount of C3d on the PNH erythrocytes of our patient appears less than that of some PNH patients on eculizumab (Figure 1C; current report). In contrast, C3d-positive erythrocytes were undetectable in PNH patients before eculizumab treatment (Figure 1C). The amount of C3d on erythrocytes may inversely correlate with the intensity of intravascular hemolysis. It then led us to speculate that intravascular hemolysis is too rapid to allow extravascular clearance of C3d-bound PNH erythrocytes in vivo. It is also theoretically possible that eculizumab-associated extravascular hemolysis is controllable by decreasing the dose of eculizumab. The C3d deposition could also be affected by the altered expression of erythrocyte glycolipids. In general, infection amplifies both intravascular hemolysis of PNH and extravascular hemolysis of hereditary spherocytosis. Eculizumab may not completely eliminate the infection-associated precipitation of hemolysis in PNH patients having both types of hemolysis.

The findings in our exceptional PNH patient surely promote unveiling of complex pathophysiology and contribute to the establishment of a better terminal complement-targeted therapy in PNH.

**Figure 1. Analysis of the C9-deficient patient with PNH.** (A) Clinical profile of the C9-deficient patient with PNH. ND indicates not determined; and PNH erythrocytes, negative for both CD55 and CD59. (B) Correlation between LDH levels and PNH type III erythrocytes (%). ○, 14 patients with PNH; ●, C9-deficient patient with PNH; dashed line, upper limit of normal LDH range. (C) C3d expression on erythrocytes of PNH patients with C9 deficiency (C9–PNH), with eculizumab (Ecu–PNH), without eculizumab (Ecu+PNH), and of a patient with autoimmune hemolytic anemia (AIHA). Numbers indicate the population (%) of cells in each quadrant. (D) Arrow indicates a PIGA mutation, deletion of G (352), in the granulocyte genome exon 2 of C9–PNH. (E) Arrows indicate urine hemosiderin stained with Prussian blue of C9–PNH.

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