

AL AMYLOIDOSIS IN A PATIENT WITH SEVERE HEMOPHILIA A AND INHIBITORS WHO HAD A MONOZYGOTIC TWIN: SAME GENES, DIFFERENT OUTCOMES

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Background. Severe hemophilia A with inhibitors has been associated, in the “pre-emicizumab era”, with high bleeding risk and complex management. AL amyloidosis is a rare plasma cell dyscrasia characterized by monoclonal light chain deposition with systemic involvement. We report a case of AL amyloidosis in a patient with severe hemophilia A and high-titer inhibitors, who had a monozygotic twin.

Case Report. The patient and his monozygotic twin were referred to our center in 1973 at the age of 10 for severe hemophilia A; the proband had developed high-titer inhibitor after repeated exposure to pdFVIII and blood products and was subsequently treated with bypassing agents. Molecular analysis identified the F8 splice-site mutation c.1537+1G>A. In 1991 he tested positive for HCV, with spontaneous viral clearance. In 1995, a first immune tolerance induction (ITI) attempt with the Malmö protocol failed. The following years were complicated by multiple bleeding episodes, but the patient repeatedly refused a second ITI course. After two iliopsoas hematomas in 2010 and 2014, he agreed to a second ITI course with pdFVIII/vWF concentrate (100 IU/kg/day), started in July 2014. A transient inhibitor increase occurred, peaking at 1715 BU after two weeks. In August 2014 he experienced severe diffuse abdominal bleeding requiring large amounts of rFVIIa. Subsequently, no fur-

ther bleeding events occurred and the inhibitor progressively declined to <1 BU in October 2016; pdFVIII/vWF was then tapered to 40 IU/kg/day by March 2017. During the 2014 hospitalization, laboratory tests revealed IgD- λ monoclonal gammopathy, with κ/λ ratio 0.04 and urinary λ Bence-Jones proteinuria of 195 mg/24 h. The patient declined further evaluation. In August 2016 he developed heart failure with reduced ejection fraction and concentric left ventricular hypertrophy. Periumbilical fat biopsy confirmed AL amyloidosis, and treatment with bortezomib, cyclophosphamide, and dexamethasone was started. In April 2017, a few days after treatment initiation, the patient died from sudden cardiac death. The monozygotic twin never developed inhibitors and presented only a stable lambda monoclonal gammopathy without organ involvement; he later developed cholangiocarcinoma.

Conclusions. We describe the rare coexistence of severe hemophilia A with inhibitors and AL amyloidosis in a monozygotic twin whose brother never developed inhibitors, suggesting that genetic background alone is insufficient to explain inhibitor development. Our question has remained if previous cyclophosphamide exposure and immune stimulation during ITI may have contributed to clonal progression. Environmental factors may therefore have influenced these divergent clinical histories: same genes, different outcomes.