



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 also a high-titer inhibitor, developed after repeated treatment with pdFVIII and blood components. He was subsequently managed with bypassing agents. Molecular analysis later identified a F8 splice-site mutation (c.1537+1G>A). In 1991, the patient tested positive for HCV with spontaneous viral clearance. In 1995, a first immune tolerance induction (ITI) attempt using the Malmö protocol failed. Thereafter the clinical course was complicated by multiple major bleeding events; nevertheless the patient repeatedly refused a new ITI course. After two iliopsoas hematomas, the first in 2010 and the second in 2014, he agreed to a second ITI course, initiated in July 2014 using pdFVIII/vWF concentrate (100 IU/kg/day). A transient inhibitor rise was observed, reaching a peak of 1715 BU after two weeks from ITI start. In August 2014 a severe episode of diffuse abdominal bleeding occurred, treated with large amount of rFVIIa in the emergency department. Thereafter, no further hemorrhagic events were reported, and the inhibitor titer progressively declined, reaching <1 BU in October 2016. Then, pdFVIII/vWF concentrate was tapered until reaching a dose of 40 IU/Kg/day in March 2017. In August 2014, during the hospitalization, laboratory in-

vestigations revealed an IgD-lambda monoclonal gammopathy, with a kappa/lambda free light chain ratio of 0.04 and urinary lambda Bence-Jones protein excretion of 195 mg/24 h. The patient was a physician and at that time declined further evaluation of the monoclonal gammopathy. Two years later, in August 2016, the patient was diagnosed with heart failure with reduced ejection fraction and concentric left ventricular hypertrophy. Cardiac magnetic resonance imaging was suggestive of transthyretin amyloidosis, although AL amyloidosis could not be excluded. A periumbilical fat biopsy confirmed AL amyloidosis diagnosis, and treatment with VCD (bortezomib, cyclophosphamide, and dexamethasone) was initiated. A few days after starting therapy, in April 2017, the patient died from sudden cardiac death. We report that the twin brother never developed an inhibitor and has a lambda monoclonal gammopathy without evidence of organ involvement. Finally, the last year he developed a cholangiocarcinoma.

Conclusions. This case shows the rare coexistence of severe hemophilia A with inhibitors and AL amyloidosis in a monozygotic twin, whose brother did never develop an inhibitor. This suggests that genetic background alone is not sufficient to determine the inhibitor event. Moreover, as regards the AL amyloidosis, we could speculate if previous treatment with cyclophosphamide, but also the immune stimulation during ITI may have contributed to clonal progression; otherwise his twin brother without inhibitor present a stable monoclonal gammopathy and developed a cholangiocarcinoma. Environmental factors could have had an impact on these divergent clinical histories: same genes, different outcomes.