Primary Factor VII Deficiency

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Although congenital Factor VII deficiency is the most common recessively inherited factor deficiency, it is a rare disease. Fewer than 200 cases of true Factor VII have been reported since it was first described in 1951. Its prevalence is equal among males and females and is estimated at 1:500,000, accounting for approximately 0.5% of all inherited coagulation disorders. Both qualitative and quantitative forms of FVII have been recorded. We report a rare case of primary FVII deficiency in an elderly patient with hematuria.

Patient Description

A 77 year old retired male tour guide of North African descent presented with painless hematuria and anemia. Past history included a single self-limiting episode of hematuria 2 years earlier; cystoscopy had been performed and the results were normal. Current examination of the patient was unremarkable except for several subcutaneous hematomata. Laboratory studies revealed hemoglobin 7.3 g/dl, mean corpuscular volume 98.9 μm^3, prothrombin time 16.1 sec, activated partial thromboplastin time 29.7 sec, and international normalized ratio 1.61. Liver function tests were within normal limits, as was renal tract sonography. The patient refused to undergo cystoscopy. He was treated with a blood transfusion and his hematuria resolved within 3 days of placement of a three-way urinary catheter. Further investigation of prolonged PT included a vitamin K challenge test that did not bring about any reduction in PT, thereby excluding vitamin K deficiency. A mixing test with normal plasma did succeed in reducing PT, thereby excluding circulating antibodies to FVII. Suspicion of a primary FVII deficiency was confirmed by an assay of procoagulant FVII activity, which measured 21.4%.

Comment

FVII is synthesized in the liver and secreted as a single-chain glycoprotein of 48 kD. It is coded by the gene on band 13q34, located close to the gene for Factor X. FVII has the shortest half-life of all procoagulant factors, being the first to decrease when there is a problem in synthesis. The hallmark of FVII deficiency is prolonged PT. The vast majority of cases of FVII deficiency are acquired. FVII deficiency most commonly results from reduced liver function or vitamin K antagonism treatment (coumarins). Acquired FVII deficiency is rarely attributed to vitamin K deficiency, to autoantibodies to FVII (associated with either autoimmune disease or malignancy), or to treatment with penicillin or cephalosporins [1].

FVII deficiency is considered to be associated with bleeding only in moderate to severe deficiency [1]. Patients with moderate deficiency (FVII activity 5–15%) typically present with mucosal bleeding such as menorrhagia, epistaxis, hematuria and melena. These features, more typical of platelet dysfunction than a coagulation defect, may be attributable to the role of the FVIIa-tissue factor complex in generating prothrombinase activity to provide thrombin for platelet activation. Symptoms similar to those seen in severe hemophilia such as hemarthrosis or intracerebral hemorrhage are encountered only in severe deficiency (< 1%) [1,2]. Moreover, there appears to be a lack of correlation between clinical symptoms and FVII levels, reflecting the existence of immunological variants of FVII deficiency [2]. In the functional FVII variant, Padua 1, bleeding symptoms are mild or absent despite a severe degree of deficiency. No excessive bleeding was reported when challenged with surgical procedures in a recent case series of patients with severe FVII deficiency [3]. Taken together, these findings suggest that clinical history is the most valuable tool in predicting the likelihood of bleeding and that perhaps not all patients with severe FVII deficiency should receive replacement therapy before surgery [4].

Molecular studies of the FVII gene in North African Jews with FVII deficiency revealed a C to T substitution at nucleotide 10648 of the FVII gene (Ala244Val) [5]. This allele, associated with decreased FVII activity and antigen level, has a frequency of 1:42 among Moroccan Jews. Similar rates are found among Iranian Jews. Since Moroccan Jews have been separated from Iranian Jews for more than two millennia, the Ala244Val mutation probably occurred in ancient times [5]. Although no genetic studies were performed, our patient could conceivably possess this allele.

Regarding the above case, it is difficult to attribute hematuria and anemia to mild

FVII = Factor VII
PT = prothrombin time

FVII deficiency. Indeed one must exercise caution in attributing mucosal bleeding to only mild deficiencies. Nevertheless, a retrospective evaluation of the patient's chart revealed that prolonged PT was previously overlooked, suggesting that FVII deficiency may be an underdiagnosed deficiency requiring a high degree of suspicion.

References

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