Factor X Deficiency

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ABBREVIATIONS: PT - prothrombin time, aPTT – activated partial thromboplastin time, INR – international normalized ratio.

INDEX TERMS: Factor X Deficiency, amyloidosis, vitamin K deficiency.

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PATIENT

52-year old Caucasian female who initially presented with lower abdominal discomfort. Evaluation included a urinalysis which was 4+ positive for protein. A 24-hour urine demonstrated 7.7 gm of protein/24 hours. Prior to undergoing a renal biopsy, a prothrombin time (PT) and activated partial thromboplastin time (aPTT) were ordered and the patient was noted to have an elevated PT of 22.4 seconds (normal range 10.0 – 13.0 sec) with an INR of 2.12 and a normal aPTT.

CLINICAL HISTORY

The clinical history is otherwise not remarkable. She underwent transabdominal hysterectomy and bilateral salpingoophrectomy and cystocele repair 6 years previously without any bleeding complications or report of abnormal laboratory screening assays. She had undergone tooth extractions without bleeding and did not suffer menorrhagia, epistaxis or easy bruisability.

FAMILY HISTORY

No family history of bleeding dyscrasias.

MEDICATIONS

None

PHYSICAL EXAMINATION

Unremarkable with the exception of 2+ pitting edema of the lower extremities

INITIAL WORK-UP

Laboratory Data (Initial)		Reference Interval
PT	22.4	10–13 sec
aPTT	31.1	23.7–37.7 sec
Factor VII	167%	50–155%
Factor II	146%	75–134%
Factor V	210%	70–150%
Factor X	25%	65–135%

PT mixing studies showed evidence of correction into the reference range consistent with a factor deficiency. FX activity repeated on a new plasma sample at another laboratory yielded a result of 32% (reference interval 65–135%).

DIFFERENTIAL DIAGNOSIS

1. *Acquired FX deficiency:* An acquired factor X deficiency is the most likely diagnosis as the patient does not have a history of bleeding and was not known to have abnormal APTT and/or PT in the past. Isolated acquired FX deficiency raises the possibility of amyloidosis which is most commonly a complication of an underlying plasma cell dyscrasia. Factor X activity could also be decreased in an acquired fashion due to a factor X inhibitor although normal plasma mixing studies would typically not show evidence of correction.
2. *Hereditary FX deficiency*: this seems unlikely given that the patient has no previous history of bleeding and there is no family history of such.

3. *Vitamin K deficiency*: While factor X may be decreased with vitamin K deficiency, this would not explain an isolated deficiency of factor X. With vitamin K deficiency, all vitamin K-dependent factors; specifically factors II, VII, IX and X decrease. Laboratory evaluation revealed that factors II and VII are normal to slightly elevated.
4. *Liver disease*: Although factor X may decrease with significant liver disease, this would not explain an isolated factor X deficiency. With liver disease (or vitamin K deficiency/antagonism), factor VII is usually the first factor to decrease as it has the shortest half life of all procoagulant factors produced in the liver. With significant liver disease, factor X is decreased as are all other procoagulant factors, specifically factor XI, IX, VII, V, X and II, except for factor VIII which may be elevated.

ADDITIONAL WORK-UP

The most common causes of nephrotic syndrome include underlying diabetes, autoimmune disease (e.g. systemic lupus erythematosus), significant liver disease or pre-existing renal disease, none of which were evident in this case. Due to the isolated low factor X activity, especially in the presence of nephrotic syndrome, a diagnosis of amyloidosis was immediately considered.

Serum protein electrophoresis revealed 1.2 gm/dL of a monoclonal protein. Serum immunoelectrophoresis demonstrated an IgG lambda monoclonal protein. Both monoclonal IgG-λ and free lambda light chains were detected in her urine. A bone marrow biopsy demonstrated 30% plasma cells with lambda restricted immunostaining, establishing the diagnosis of myeloma. Congo red stains of the bone marrow biopsy and of the aspirate of abdominal wall fat were negative for amyloidosis. Radiographic skeletal survey did not demonstrate either osteolytic lesions or osteoporosis.

High dose dexamethasone therapy resulted in a decrease in both proteinuria and serum paraprotein. The patient developed severe epigastric symptoms associated with this therapy. Esophagogastroduodenoscopy revealed no significant mucosal lesions but biopsies demonstrated amyloidosis in the mucosa of both the stomach and duodenum. At this time, she developed severe liver function test abnormalities, progressive hepatomegaly and ascites, and computerized tomography that suggested cirrhosis of the liver.

DIAGNOSIS

Multiple myeloma complicated by systemic amyloidosis (AL) resulting in nephrotic syndrome.

MANAGEMENT APPROACH

The patient was begun on dexamethasone, melphalan, bortezomib. Two years later the patient was doing exceedingly well and is totally asymptomatic, her PT normalized, serum creatinine decreased from 1.7 to 1.0 mg/dL, total IgG decreased from 1722 mg/dL to 247 mg/dL and monoclonal protein concentration decreased from 1.17 g/dL to 0.21 g/dL. The ascites resolved and liver size returned to normal. Moderate proteinuria persists.

GENERAL DISCUSSION

The most common form of amyloidosis is light chain amyloidosis (AL). In this instance, the amyloid fibrils are composed of IgG light chains or light chain fragments produced by a clonal population of plasma cells. Approximately 10 – 15 % of patients with myeloma or Waldenstrom macroglobulinemia develop systemic AL. The diagnosis of AL amyloidosis requires 1) demonstration of amyloid in tissue and 2) demonstration of a plasma cell dyscrasia. Evaluation often includes investigation of serum and urine for monoclonal light chains and a bone marrow biopsy as well as Congo red staining of an involved tissue or random abdominal fat or rectal biopsy. Organs most commonly involved in systemic amyloidosis include the kidney and heart. Renal involvement usually manifests as nephrotic syndrome. Amyloid may also deposit in the gastro-intestinal tract, liver and peripheral nervous system. The majority of patients with AL have 1 or 2 organs involved and about 30% have 3 or more major organ systems involved.

Acquired factor X deficiency is the most common coagulation factor deficiency identified in AL amyloidosis and it occurs presumably as a result of adsorption of factor X to amyloid deposits. Decreased factor X levels in AL occurs independent of hepatic parenchymal disease and as in this case, may occur as an

isolated factor deficiency. Due to the well known correlation of factor X deficiency with AL, it has been recommended that once a diagnosis of AL is made, all patients should be screened for factor X deficiency. A study of 368 new patients with AL revealed an incidence of factor X deficiency in 8.7% or 32 patients. Of these 32 patients, over half had bleeding complications and in two, the hemorrhage proved fatal. Bleeding severity correlated with factor X levels and those with <25 % factor X activity were more likely to bleed. Successful aggressive treatment of the underlying plasma cell dyscrasia is associated with improvement in factor X activity levels and even partial hematologic responses may show improvement of factor X levels. Aggressive therapy employing high dose chemotherapy with stem cell rescue has been used effectively to treat AL. In patients with splenomegaly, splenectomy has been reported to acutely improve factor X levels, presumably due to removal of a large amyloid pool. In the acutely bleeding patient or in a patient requiring surgical intervention, fresh frozen plasma or recombinant activated factor VII may be of benefit.

Acquired isolated factor X deficiency may also occur secondary to a specific factor X inhibitor. These inhibitors are rare and may arise without provocation or may occur in association with underlying infections, such as leprosy. Laboratory evaluation typically demonstrates an elevated APTT and PT with incomplete correction in plasma mixing studies. Factor X inhibitors can be quantified using the Bethesda assay. Clinically, the majority patients with factor X inhibitors present with bleeding and factor X levels in the range of 1 to 20%.

Hereditary factor X deficiency is a rare autosomal recessive, hemorrhagic disorder with a reported incidence of about one in one million. Patients with severe deficiencies (<1%) typically present with bleeding early in life, including hemarthroses, gastrointestinal bleeding, hematuria and CNS hemorrhage. Those with less severe deficiencies are often asymptomatic and may bleed only after challenged.

The diagnosis of factor X deficiency is based on measurements of factor X activity, typically using a clot-based assay, although a chromogenic factor X activity assay could be used. Typically both the APTT and PT are prolonged in patients with factor X deficiency. With less severe deficiencies, as in this case however, the PT may be prolonged while the APTT falls in the normal range as most PT reagents are more responsive to mild deficiencies of factor X than are APTT reagents.

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