

CASE REPORTS

Factor VII deficiency in systemic primary amyloidosis: A rare case

Fadime Ersoy Dursun*¹, Erdal Akyar², Gokhan Uygun², Zafer Baslar³, Bengu Cobanoglu⁴

¹Department of Hematology, Istanbul Medeniyet University Goztepe Training and Research Hospital, Istanbul, Turkey

²Department of Internal Medicine, Istanbul Medeniyet University Goztepe Training and Research Hospital, Istanbul, Turkey

³Department of Hematology, Istanbul University Cerrahpasa Medical Faculty, Istanbul, Turkey

⁴Department of Pathology, Istanbul Medeniyet University Goztepe Training and Research Hospital, Istanbul, Turkey

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ABSTRACT

Introduction: Isolated and combined factor deficiencies are known to occur in systemic primary amyloidosis. The most common factor deficiency known in these cases is isolated factor X deficiency. Other factor deficiencies are relatively less frequent. Isolated factor VII deficiency occurs very rarely in cases of systemic primary amyloidosis.

Case report: A 58-year-old male patient previously presenting to another health center with complaints of generalized edema, fatigue, and itching had proteinuria and then he was diagnosed with systemic primary amyloidosis after the renal biopsy for proteinuria etiology. The patient's laboratory tests showed prolongation of prothrombin time and factor VII deficiency. The patient responded well to the treatment for primary amyloidosis and factor VII deficiency.

Discussion: In cases of systemic primary amyloidosis, if the etiology of prolonged prothrombin time involves no liver disease, warfarin use, or malabsorption, physicians should always keep in mind rare factor deficiencies such as factor VII deficiency, along with common factor deficiencies.

Key Words: Systemic primary amyloidosis, Isolated factor VII deficiency

1. INTRODUCTION

Amyloidosis refers to a group of rarely seen serious diseases caused by accumulation of an abnormal protein called "amyloid" in human tissues and organs. Systemic amyloidosis types are categorized as primary, secondary, or familial (inherited). Primary amyloidosis (AL) is the most prevalent type of systemic amyloidosis. In secondary amyloidosis (AA), the inflammatory protein is derived by serum amyloid A.^[1]

Coagulation factor deficiencies are common in cases of systemic primary amyloidosis.^[2] Combined factor deficiencies

like factor IX-factor X or factor VII-factor X are rarely reported in these patients, while isolated factor II, factor V, and factor IX deficiencies are often occurrences.^[3-5] Isolated factor VII deficiency is a quite rare condition in amyloidosis, and just one case has so far been reported in the literature.^[6] Conditions associated with rare clotting disorders, such as factor VII deficiency, in these patients, are often overlooked, or go unrecognized. Hereditary factor VII deficiency is categorized as type 1 or type 2 based on the finding that whether factor VII antigen exists in the plasma. Type 1 deficiencies are caused by a reduction in biosynthesis or acceleration in

*Correspondence: Fadime Ersoy Dursun; Email: drfadimeersoy@yahoo.com.tr; Address: Department of Hematology, Istanbul Medeniyet University Goztepe Training and Research Hospital, Istanbul, Turkey.

clarify; Type 2 abnormalities, on the other hand, represent a dysfunctional molecule. Today, classification depending on patient's clinical history including age and presentation type of the patient instead of factor VII activity levels has been shown to be a more valuable tool in determining future bleeding risks.^[5,6] Here we report a rare case of isolated factor VII deficiency, detected while the patient was tested for prolongation of prothrombin time (PT) associated with systemic primary amyloidosis. We obtained a written informed consent from the patient for this case report.

2. CASE REPORT

A 58-year-old male patient previously presenting to another health center with complaints of generalized edema, fatigue, and itching had proteinuria and then he was diagnosed with systemic primary amyloidosis after the renal biopsy for proteinuria etiology. The patient was referred to our department and then hospitalized for further examination and treatment. The patient reported no history of chronic diseases in family, and the coagulation test results were normal and he had no history of bleeding disorders.

The general condition of the patient was moderate-to-good; his vital findings were stable, and he was fully conscious, oriented, cooperative, with pale skin and generalized edema, as well as pretibial pitting (+++) edema (see Figure 1a). Examinations of the head and neck, eyes, ears, nose, throat, respiratory, cardiovascular, and genitourinary systems were normal. In his examination of the gastrointestinal system, there was abdominal distention and tenderness, as well as acid in the area extending from the lower abdomen to the umbilical region (see Figure 1b). The bowel sounds were natural, with no rebound, guarding, hepatomegaly and splenomegaly, and other system examinations were normal.

The results of laboratory tests and normal values are shown in Table 1. His leukocyte count was 8,300/mm³, absolute neutrophil count 4,870/mm³, hemoglobin 10.4 gr/dl, hematocrit 32%, platelets 222,000/mm³, PT 17.9 sec, active partial thromboplastin time 34 sec, and INR 1.48. Biochemical analyses showed an urea level of 45 mg/dl, creatinine 0.73 mg/dl, total protein 4.5 g/dl, albumin 1.8 g/dl, aspartate aminotransferase 22 IU/L, alanine aminotransferase 6 IU/L, gamma glutamyl transferase 143 IU/L, alkaline phosphatase 266 IU/L, lactate dehydrogenase 193 IU/L, glucose 98 mg/dl, total cholesterol 267 mg/dl, triglyceride 193 mg/dl, LDL-cholesterol 201 mg/dl, HDL-cholesterol 27 mg/dl, calcium 7.2 mg/dl, phosphorus 4.2 mg/dl, and β 2-microglobulin 6,421 ng/ml. 24 hour urine analysis of the patient revealed proteinuria levels of 6,000 mg/24 h, glomerular filtration rate 104 ml/min/1.73 m². Besides, sedimentation was 77 mm/s, c-reactive protein 0.45 mg/dl, and brain natriuretic

peptide 360 pg/ml. There was no monoclonal band on serum and urine immunofluorescence electrophoresis. Serum protein electrophoresis showed no M protein band. The initial primary amyloidosis diagnosis was supported by the bone marrow biopsy performed in our unit, and the level of plasma cells in the bone marrow was found to be less than 5% and polyclonal.

The patient's full abdominal ultrasound showed a liver cranio-caudal diameter of 186 mm and enlarged long axis of spleen measuring 168 mm. The ultrasound imaging also showed generalized free fluid in the abdomen. The positron emission tomography/computed tomography (CT scan) found no pathologic radiopharmaceutical F-18 fluorodeoxyglucose involvement or lytic bone lesion on direct CT images. In cardiac magnetic resonance imaging, there was a slight concentric hypertrophic appearance in the left ventricle; interventricular septum thickness in diastole was 14 mm and slightly above the physiological limits, and minimal effusion in the pericardial space.

The patient's elevated PT levels detected by initial tests did not improve with vitamin K treatment. No concomitant sepsis, renal insufficiency, disseminated intravascular coagulation or liver failure was detected. Mixing studies failed to confirm the presence of an inhibitor and therefore factor levels that could prolong the PT were examined (see Table 1). The Factor VII level was found to be 46% and Factor VII antigen was 52%, so isolated Factor VII deficiency was considered because these levels were below normal values. Other factor levels were normal (see Table 1). In the bone marrow biopsy specimens, eosinophilic amorphous proteinaceous deposits were observed on the vein walls and histochemical and immunohistochemical staining confirmed amyloid presence (see Figure 2). There was no bleeding complication during renal and bone marrow biopsy of the patient. Upon these findings, we decided that the patient had factor VII deficiency accompanying nephrotic syndrome and systemic primary amyloidosis. He was treated with vitamin K regimen for prolonged levels of PT, but no improvement was observed. A combination regimen of VCD (Cyclophosphamide, Bortezomib, Dexamethasone) was initiated for primary amyloidosis in the patient, as he was considered to be in the moderate risk group based on his glomerular filtration rate and proteinuria.^[2,7] After three cycles of treatment, the general condition and renal functions of the patient returned to normal, with improved edema, acid and acidosis (see Figure 1c, d). A significant reduction was achieved in the proteinuria of the patient, and factor VII level (178%) and coagulation test results [PT 14.9 sec (11.5-15.5), INR 1.2 (0.8-1.25), activated partial thromboplastin time 30 sec (25.6-35.2)] returned to normal values.

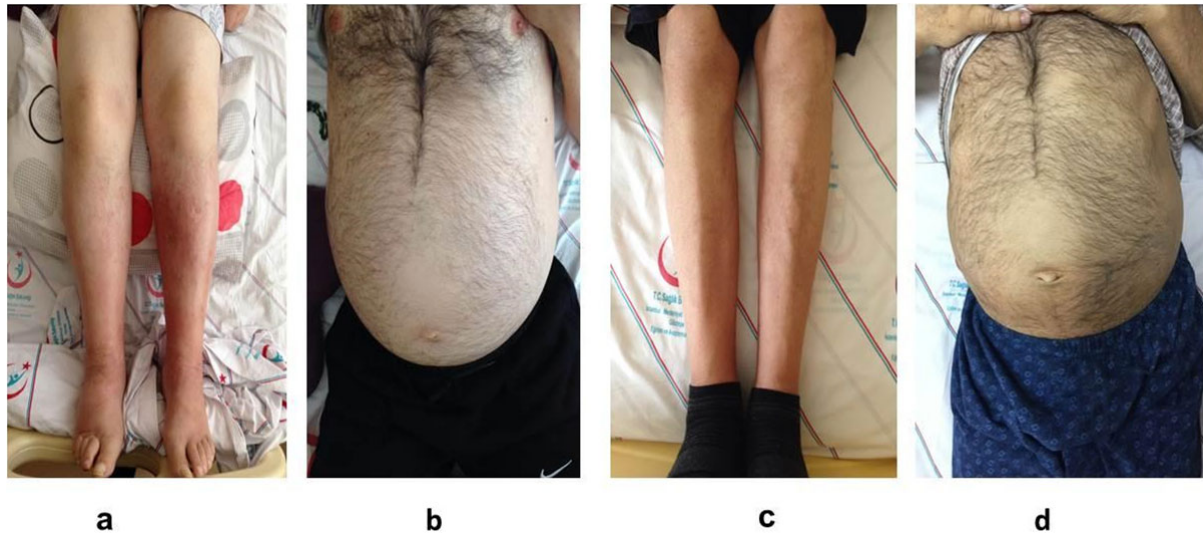


Figure 1. Ascites and pretibial edema of the patient before and after treatment. Pretibial edema (a) and ascites (b) finding before treatment, Pretibial edema (c) and ascites (d) finding after treatment.

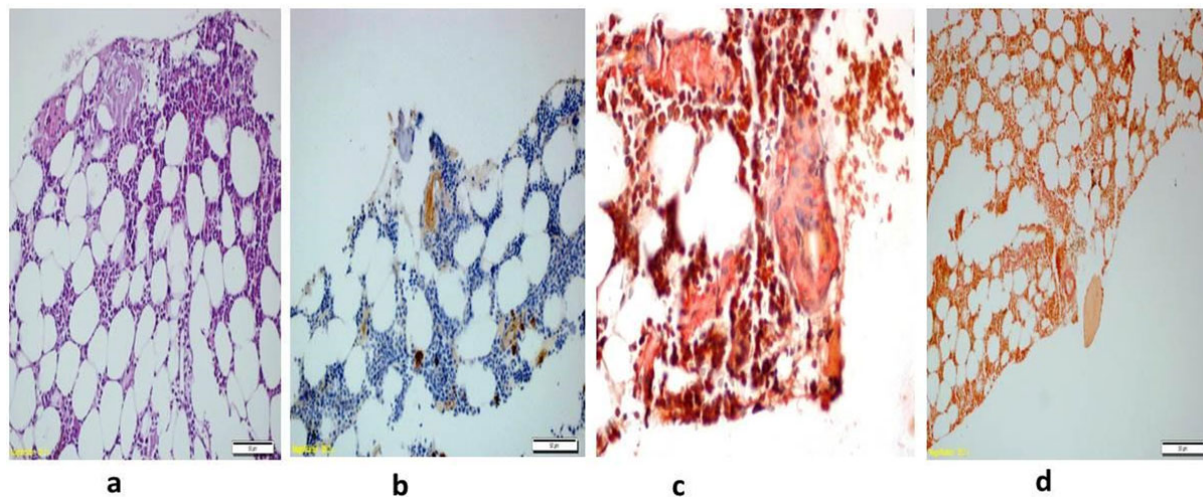


Figure 2. Bone marrow biopsy specimen; a. The accumulation of proteinaceous material in the wall of vascular structures HE $\times 200$, b. immunohistochemical Amyloid A staining AA protein $\times 400$, c. Histochemically, Congo red staining $\times 400$, d. Histochemically Permanganant Congo $\times 400$.

3. DISCUSSION

Acquired factor X deficiency in patients diagnosed with amyloidosis is well defined; however, cases of acquired factor VII deficiency are quite rare in the literature. Hemorrhage is known to be a typical symptom of systemic primary amyloidosis and can be a serious problem. Approximately one-third of the patients exhibit bleeding symptoms and about half of the patients show abnormal clotting findings.^[8] Although the most common symptom of hemorrhage is purpura because of increased vascular fragility resulting from the deposition of endothelial amyloid material, life-threatening bleeding following liver or kidney biopsy is a well-established find-

ing, with another characteristic finding of periorbital purpura (“raccoon eyes”).^[8] Previous works in the literature have reported that clotting factors regulating blood clot formation are amyloid-dependent and certain improvements were achieved in haemostasis once the spleen had been removed because it was severely infiltrated by amyloid material.^[9] Most of the coagulation abnormalities have been explained by poor fibrin polymerization or a decrease in factor X activity. However, the literature includes several studies reporting that coagulopathy was reversed following cytotoxic chemotherapy.^[10] Even though our patient showed no significant bleeding symptoms, we detected that he had pro-

longed PT. Based on this finding, we managed to diagnose the patient with factor VII deficiency, which is a very rare occurrence in the literature.

Table 1. Laboratory findings of patient

Parameters (unit)	Results	Reference intervals
Leukocyte (mm ³)	8,300	4,000-10,000
ANC (mm ³)	4,870	1,400-6,500
Hemoglobin (gr/dl)	10.4	13-17
Hematocrit (%)	32	40-54
Platelets (mm ³)	222,000	150,000-500,000
Prothrombin time (sec)	17.9	11.5-15.5
aPTT (sec)	34	25.6-35.2
INR	1.48	0.8-1.25
Urea (mg/dl)	45	18-55
Creatinine (mg/dl)	0.73	0.72-1.25
GFR (ml/min/1.73 m ²)	104	> 90
Total proteine (gr/dl)	4.5	6.4-8.3
Albumine (gr/dl)	1.8	3.5-5.2
AST (IU/L)	22	< 37
ALT (IU/L)	6	< 42
GGT (IU/L)	143	< 64
ALP (IU/L)	266	< 150
LDH (IU/L)	193	125-220
Glucose (mg/dl)	98	70-105
Total cholesterol (mg/dl)	267	< 200
Triglycerides (mg/dl)	193	<150
LDL-cholesterol (mg/dl)	201	<130
HDL-cholesterol (mg/dl)	27	35-65
Calcium (mg/dl)	7.2	8.4-10.2
Phosphorus (mg/dl)	4.2	2.3-4.7
Sedimentation (mm/h)	77	< 15
CRP (mg/dl)	0.45	0-05
Brain NP (pg/dl)	360	0-100
β ₂ -microglobuline (ng/ml)	6,421	< 2,500
Factor II (%)	110	50-150
Factor V (%)	84.6	“
Factor VII (%)	46	“
Factor IX (%)	70.4	“
Factor X (%)	91	“
Factor XI (%)	64	“
Factor XII (%)	77.7	“
vWF (%)	199.5	“
vWF ristocetin cofactor (%)	184.4	“
Factor VII antigen (%)	52	70-120
24 hours urine proteine (mg/24h)	6,000	0-150

Note. ANC: Absolute neutrophil count, aPTT: Activated partial thromboplastin time, INR: international normalised ratio, AST: Aspartate amino transferase, ALT: Alanine amino transferase, GGT: gamma glutamyl transferase, LDH: lactate dehydrogenase, CRP: C-reactive protein, vWF: von willebrand factor

Factor VII deficiency may be inherited or acquired. Inherited factor VII deficiency is known to be a rare but serious au-

tosomal recessive bleeding condition. Blood clotting factor VII is a coagulation factor dependent on vitamin K and is synthesized in the liver. It is usually found in human plasma at low concentrations (0.5 mcg/ml) with a relatively short half-life of 3-4 hours in the circulation. Factor VII is often found in the shape of an inactive single-chain zymogen. Nevertheless, it is present in the circulation at the rate of 1% in an activated form (FVIIa). The activation of Factor VII initiates a series of extracellular coagulation events.^[11,12] A defect such as Factor VII deficiency could occur with mild-to-moderate severity and may present itself with a minor prolongation in the PT. If physicians do not run certain coagulation factor tests to further investigation of isolated PT prolongation, they may not diagnose the condition accurately. We detected isolated factor VII deficiency in a patient recently diagnosed with systemic primary amyloidosis who had mild-to-moderate, isolated PT prolongation and no bleeding symptom.^[13-15] In the relevant literature, there is no study reporting any case of isolated factor VII deficiency in systemic primary amyloidosis, except for the one reported by Uematsu et al.^[5]

Current guidelines lack any evidence-based treatment options for hemorrhaging in amyloidosis patients.^[7] The evidence level for all the available recommendations is 4C. In cases of bleeding, traditional supportive therapies should be administered, which may include the replacement of the deficient factor determined by clotting tests and platelet transfusion when thrombocytopenia is considered to contribute to bleeding based on platelet count. In addition, antifibrinolytic agents and local precautions can be utilized to achieve haemostasis.^[2,7] In light of these recommendations in the literature, we treated our patient with 3 cycles of VCD chemotherapy protocol. The patient's response to this treatment was good at the clinical and laboratory levels. The patient is still monitored in our clinic.

4. CONCLUSION

In conclusion, we decided to report this case in order for physicians to keep in mind the isolated factor VII deficiency in systemic primary amyloidosis patients. This case demonstrates the importance of meticulous evaluation of coagulation tests. Therefore, in cases of systemic primary amyloidosis with no liver disease, warfarin use, or malabsorption, physicians should always consider rare factor deficiencies such as factor VII deficiency, along with more common factors like Factor X, if the patient has prolonged PT.

CONFLICTS OF INTEREST DISCLOSURE

The authors have declared no conflicts of interest.

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