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Acquired Factor X Deficiency Associated with Systematized Amyloidosis—A Report of a Case

By Margaret Howell

COAGULATION DEFECTS due to the lack of a single blood clotting factor are almost exclusively congenital and symptoms appear in early life. Acquired defects other than iatrogenic are usually the result of liver dysfunction and in such cases more than one clotting factor is depressed. A case of selective factor X deficiency developing in middle life and associated with extensive amyloidosis has recently been described.[1] The present report concerns a middle-aged man who presented with spontaneous bruising of 3 months duration; the abnormal bleeding tendency was due to a pure factor X deficiency, and the patient was subsequently found to have systematized amyloidosis.

Case History

The patient, a 51 year old man, gave a 4 month history of spontaneous bruising and excessive bleeding following minor trauma. There was no family history of bleeding, no previous history of spontaneous hemorrhage, and dental extractions in the past had not caused excessive blood loss. He had no other complaints, but had lost about 8 lb. over a period of 3 months despite a normal appetite. There was an enlarged gland in the left axilla: the liver was enlarged five fingersbreadth below the costal margin and was smooth but not tender. There were no other abnormal physical findings.

Investigations

Hb 12.3 Gm./100 ml. (84 per cent); MCHC 31 per cent; ESR (Wintrobe) 39 mm. in 1 hour; WBC 11,200/cu.mm.; blood film normal. Plasma bilirubin 0.3 mg./100 ml.; plasma alkaline phosphatase 26 King-Armstrong units; thymol turbidity 1 unit; blood urea 25 mg./100 ml.; total protein 7.3 Gm./100 ml.; electrophoresis showed slight increase in the α_2 globulins; plasma acid phosphatase (formol stable) 5 units (this was repeated and was 3.9 units); Wasserman reaction and Kahn were negative. Urine: albumin +; red cells +; no pus cells, casts or organisms. Chest x-ray normal. Hemostatic mechanisms: Bleeding time (Duke), 1 minute; clotting time (Lee and White), 13 minutes; platelets 232,000/cu.mm.; Hess test (tourniquet at 90 mm. Hg for 5 minutes), negative; single stage prothrombin time[2] using a saline extract of human brain, 39–53 seconds (control, 13 seconds); stypven time, Russell's viper venom in 1 per cent ovolecithin in saline, 15.5 seconds (control, 6.5 seconds); thrombin time, 12 seconds (control 10 seconds); Fibrinogen, 0.47 Gm./100 ml.; blood clot lysis time (Fearnley), 4 hours.

The thromboplastin generation test[3] was performed using platelet substitute.[4] The results (table 1) show that there is a defect of the patient's serum but that his adsorbed plasma is normal. Cross-correction experiments were carried out in order to characterize

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Table 1.—*Thromboplastin Generation Test*

Incubation time after recalcification (minutes)	2	3	4	5	6	7
Normal plasma Normal serum Platelet substitute	60.0	37.5	17.0	11.5	10.5	10.0
Patient's adsorbed plasma Normal serum Platelet substitute	37.0	13.5	10.0	9.25	8.5	9.0
Normal adsorbed plasma Patient's serum Platelet substitute	—	88.5	77.5	75.0	80.0	—
Patient's adsorbed plasma Patient's serum Platelet substitute	—	95.0	81.5	78.5	79.5	47.5

The recorded figures represent the clotting times in seconds of the substrate plasma to which samples of the incubation mixture have been added.

Table 2.—*Correction of Patient's Plasma by Normal Serum and Factor VII-deficient Plasma*

Test Material	Prothrombin time (seconds)
Normal plasma (control)	13.5
Patient's plasma	43.0
Patient's plasma (9 parts) + normal serum (1 part)	23.5
Patient's plasma (1 part) + normal serum (1 part)	15.0
Patient's plasma (1 part) + deficient plasma (< 2% factor VII) (1 part)	15.0

Table 3.—*Correction of Factor IX-deficient Plasma by the Patient's Serum*

Incubation time after recalcification (minutes)	ml.	4	5	6	7
IX-deficient plasma Platelet substitute	0.5 0.5	120	102	107	—
IX-deficient plasma Patient's serum Platelet substitute	0.4 0.1 0.5	10	9	10	—
Patient's plasma Patient's serum Normal serum Platelet substitute	0.30 0.24 0.06 0.6	39	18	11	10

The recorded figures represent the clotting times in seconds of the substrate plasma to which samples of the incubation mixture have been added. All plasma and serum was diluted 1:9 in Owren's buffer before use in incubation mixture.

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the defect further. The results shown in tables 2 and 3 reveal that there was no significant deficiency of factors II (prothrombin), VII, or IX.

Results

That this was factor X deficiency was confirmed, as the patient's plasma failed to correct known factor X-deficient plasma.* Assay showed the level of factor X to be less than 2 per cent.[5]

In order to perform liver biopsy an attempt was made to remedy the patient's clotting defect. Vitamin K_1, 10 mg. daily intravenously for 5 days, did not correct the prothrombin time. He was therefore rapidly transfused with 800 ml. fresh ACD plasma and 1 liter of fresh frozen plasma. His prothrombin time before transfusion was 53 seconds and after transfusion 49 seconds (control 13 seconds). These results suggested either that factor X was being destroyed or that its activity was inhibited in the patient. The following in vitro experiment failed to show any inhibition: the patient's plasma was incubated at 37 C. with an equal volume of normal plasma, and the prothrombin time of this mixture at the end of 1 hour was 14 seconds (control 13 seconds).

Because of the danger of bleeding, liver biopsy was not done. Corticosteroid therapy affected neither the clinical manifestations of the disease nor the clotting capacity. His condition deteriorated and he died 5 months after the onset of symptoms. Shortly before death his white blood count was 16,000/cu. mm., 10 per cent of the cells being plasma cells. Chest x-ray showed multiple small areas of bone destruction, and marrow aspiration showed infiltration with primitive cells.

Postmortem examination revealed a liver infiltrated with amyloid, which was found to be systematized throughout the body. Lymph nodes in general were slightly enlarged, soft, and congested; the spleen was also enlarged and contained diffusely scattered nodules of tumor tissue. Similar deposits were found in the bones. Microscopy showed that the bone marrow, spleen, and lymph glands contained tumor cells with the features of primitive plasma cells. The ultimate diagnosis was myelomatosis and amyloid disease.

Discussion

In 1956 a patient (Prower) was reported with a clotting defect causing prolongation of the Quick single stage time. This was corrected by normal serum but the anomaly differed from factor VII deficiency in that there was abnormal thromboplastin generation.[6] In 1957 a similar case (Stuart) was reported[7] and subsequent work has shown Prower and Stuart factors to be identical.[8] Several further cases have been described and reappraisal of those formerly labeled as factor VII deficiency has shown some in fact to be Stuart-Prower deficiency.[9]

In 1954 and 1955 Koller and his associates, studying the blood of patients

*Factor X-deficient plasma was kindly supplied by Dr. Rosemary Biggs.

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treated with coumarin derivatives, inferred the existence of a third serum clotting factor which they called factor X.[10-13] This factor shares many but not all of the properties of Stuart-Prower, and Koller concluded that the phenomenon described as factor X was produced primarily by Stuart-Prower factor but that another factor, probably the pre-phase accelerator (PPA), might be responsible for some of its properties.[14] Nonetheless the International Committee on the nomenclature of blood clotting factors designated the Stuart-Prower factor as factor X.[15]

Factor X is apparently utilized in different ways in intrinsic coagulation, during which it is not consumed, and in extrinsic coagulation when it is used up.[16,17] It is adsorbed by aluminum hydroxide and by barium sulphate. It is stable in stored plasma for at least a month. It is depressed during therapy with the indanedione and coumarin derivatives, and as a result of biliary obstruction or severe liver disease. However, such depression is associated with depression of other clotting factors. Pure factor X deficiency is usually congenital and seems to be inherited as a highly penetrative incompletely recessive autosomal characteristic.[18]

One unusual feature in this case is the apparent acquisition of a single factor defect in adult life. It is not possible to demonstrate any cause. Amyloid disease in itself may give rise to hemorrhage but this is due to amyloid infiltration of the blood vessel walls. No defect of coagulation has been described due to amyloid disease *per se*. In a series of 73 cases, 10 who bled abnormally were investigated. Three bled into the skin and one of these had hematuria, one had hemoptysis, two recurrent epistaxis, two gross rectal bleeding, and one had occult blood in the stools. None of these patients had any demonstrable clotting defect and none had thrombocytopenia.[19] Replacement of liver tissue by amyloid infiltration might cause depression of factors II (prothrombin), V, VII and IX as well as X, and such depression only occurs when decompensation is severe: this was not so when the patient was first investigated.

The other unusual feature was the failure of transfused fresh plasma to shorten the prolonged single stage prothrombin time. Graham[20] described how he transfused his patient with 1055 ml. of ACD plasma and raised the circulating level of factor X from less than 3 per cent to 23 per cent. The prothrombin time decreased from 49.5 to 15 seconds. This level gradually dropped again, reaching 6 per cent at the end of 5 days. It seems likely that in the case now described the transfused factor X was being neutralized. However, no such inhibition of normal plasma could be demonstrated in vitro. Two other cases of acquired pure factor X deficiency have been reported. The first was thought to be due to exposure to a fungicide methyl bromide, and the patient recovered spontaneously after 44 days.[21] The other is the case referred to above and was similar to the one reported here as it was associated with amyloidosis and fresh plasma transfusions were ineffective.[1]

In the two cases associated with amyloidosis, there are three possible causes for the factor X deficiency. One is that the liver, due to amyloid in-

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filtration, was unable to form factor X. Another is that the factor was being formed normally but immediately neutralized, possibly by an abnormal circulating protein resulting from the underlying disease: this could explain inhibition of factor X in the transfused plasma. However, this should have been demonstrable in vitro. A third possibility is that the amyloid deposits were able to take up factor X selectively.

Summary

A case is described of acquired factor X deficiency in a patient with diffuse amyloidosis and myelomatosis. Rapid transfusion with fresh plasma failed to shorten the Quick single stage prothrombin time. Inhibition of factor X could not be demonstrated in the patient's plasma in vitro.

Summario in Interlingua

Es describite un caso de acquirite carentia de factor X in un patiente con diffuse amyloidosis e myelomatosis. Le rapide transfusion con plasma fresc non reduceva le tempore de prothrombina secundo le uniphasic test de Quick. Inhibition de factor X non poteva esser demonstrate in le plasma del patiente in vitro.

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