Acquired Hemorrhagic Diathesis of Unknown Nature

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A hemorrhagic diathesis is caused by disturbance of the hemostatic platelet function, the hemostatic vascular function or the clotting mechanism. Simple tests such as the whole blood clotting time, the bleeding time and the tourniquet test usually give a clue as to the nature of the hemorrhagic disorder. With more thorough investigation it is usually possible to state which of the components of the hemostatic mechanism is at fault.

A prolonged bleeding time is caused by thrombocytopenia, by a qualitative platelet defect or by a vascular disturbance, except in von Willebrand's disease in which it is most probably due to lack of a plasmatic factor (Nilsson et al. [1957a]; Nilsson et al. [1957b]).

We have recently observed a patient with a severe hemorrhagic diathesis, in whom the only pathological finding was a markedly prolonged bleeding time; extensive studies, however, failed to give any clue as to the cause of the hemostatic disorder.

Case Report

J. S., male, born 1. 7. 97, married, four healthy children. No known case of hemorrhagic disease in the family.

He had always been healthy, and had not experienced any unusual bleeding episodes until spring 1957, when he had repeated epistaxis, which, however, stopped after thermocauterization. Several years before that he had an uncomplicated operation for hemorrhoids, and he had had all his teeth extracted without abnormal bleeding.

On March 12, 1958 he was admitted to Medical Dept. A, Rikshospitalet, Oslo, because of gastric tumor and anemia. There were no petechiae or ecchymoses, and no palpable glands. Blood pressure was 125/55. The liver could be felt just below the costal margin. The spleen was not palpable. An x-ray examination

Tab. 1: Laboratory findings concerning hemostasis in the patient (with normal ranges and references for the methods).

Type of test	Results in the patient	Normal range	References for methods
Primary bleeding time	> 30 min.	3—11 min.	Borchgrevink and Waaler (1958)
Secondary bleeding time	22½ min.	1—6 min.	Borchgrevink and Waaler (1958)
Tourniquet test	no petechiæ	< 20 petechiæ	Stefanini and Dameshek (1955)
Whole blood clotting time	3 min.	2—5 min.	Hjort and Stormorken (1957)
Thromboplastin time	13 sec.	12.5—14 sec.	Borchgrevink and Waaler (1958)
PP-value	101%	75—125%	Owren and Aas (1951)
Cephalin time: First fibrin threads	39 sec.	35— 40 sec.	Waaler (1957)
Cephalin time: Firm clot	53 sec.	50— 60 sec	
Recalcification time (firm clot)	104.3 sec.	95—110 sec.	Waaler (1957)
Antihemophilic A factor	120%	75—125%	Waaler (1959)
Antihemophilic B factor	110%	75—125%	Stapp (1958)
Activation product (after maximal activation)	880%	800—1500%	Waaler (1959)
Prothrombin consumption (residual prothrombin after 2 hours)	16%	< 20%	Hjort et al. (1955)
„Thromboplastin" generation test with patient's platelets	Normal		Biggs and Douglas (1953)
Fibrinogen concentration	240 mg/ 100 ml	200—400 mg/ 100 ml	
Fibrinolysis	—	—	
Platelet count per mm^3	198 000	150—300 000	Nygaard (1933)
Number of adhesive platelets per mm^3	96 000	70—140 000	Hellem (1958)
Per cent adhesive platelets	48.5%	30—60%	Hellem (1958)
Clot retraction (after 24 hours)	8.7 cm	> 6.5 cm	Voss (1958)
Coombs test: Direct	—		
Coombs test: Indirect	—		

confirmed the presence of a tumour in the fundus of the stomach. Hb. was 8 g/100 ml. R. b. c. 3.5 mill. His stools had a constantly positive benzidine reaction.

Before referring the patient for surgery, routine tests for hemostasis were performed, and the markedly prolonged bleeding time was discovered. More thorough examination of the hemostatic function was then carried out (table 1), the only pathological finding remaining, however, a severely prolonged primary and secondary bleeding time.

As we were unable to explain the cause of the prolonged bleeding time on the basis of the findings listed in table 1, some additional studies were carried out.

Capillary microscopy revealed completely normal capillaries. His platelets showed normal morphology in the phase-contrast microscope. The addition of thrombin to his platelets produced normal viscous metamorphosis.

To see whether he was lacking a plasma factor necessary for normal hemostasis, he was transfused with 3 l of fresh blood, 1½ l of blood being removed simultaneously. The bleeding time, however, was not shortened (table 2).

Tab. 2: Bleeding time and platelet count before and after transfusion of 3 l of fresh, whole blood (1½ l of blood being removed at the same time).

	Before transfusion	Immediately after transfusion	24 hours after transfusion
Bleeding time in minutes	> 30	> 30	> 30
Number of thrombocytes per mm^3	187 000	186 000	

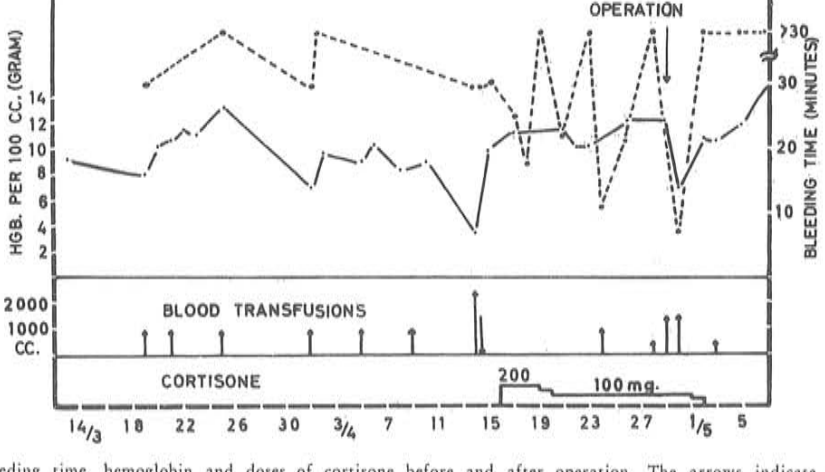
To rule out the presence of an inhibitor disturbing normal hemostasis, ½ l of his blood was given to a person with normal bleeding time. As seen in table 3, this transfusion had no effect on the bleeding time or the platelet count of the recipient.

Tab. 3: Bleeding time and platelet count in a person with normal hemostasis before and after transfusion of ½ l of blood from the patient.

	Before transfusion	Immediately after transfusion	24 hours after transfusion
Bleeding time in minutes	4½	3½	3
Number of thrombocytes per mm^3	637 000	627 000	

The patient was given cortisone, which seemed to shorten his bleeding time slightly. While on treatment, a gastric resection was performed. The tumor, the size of a tomato, proved to be an adenocarcinoma. Several small glands with metastases were also removed. A marked bleeding tendency was observed during the operation.

The first day after the operation his bleeding time was normal but it later reverted to severely prolonged values (fig. 1).



Bleeding time, hemoglobin and doses of cortisone before and after operation. The arrows indicate the time and quantity of blood transfusions.

Nine days after operation a severe intraabdominal hemorrhage occurred, and he was given 3½ l of blood. He developed acute renal failure, however, with oliguria and a steadily increasing blood urea. He died three weeks after the operation.

The post mortem examination showed: blood in the peritoneum, enlarged spleen (420 g), no detectable metastases, and hyperplasia of the bone marrow with increased megakaryocytes.

Discussion

The hemorrhagic diathesis was most probably acquired, since the patient had not experienced any pathological bleeding on extraction of the teeth, had earlier had uncomplicated surgery, and had gone through all the many minor accidents of 60 years of life without any abnormal bleeding.

The prolonged bleeding time was discovered at the same time that he developed a carcinoma of the stomach. There might have been a causal relationship between the cancer and the hemostatic disturbance, but this problem remains unsolved because the cause of the prolonged bleeding time was not determined. A platelet defect can probably be ruled out since his platelets showed normal morphology, normal adhesiveness to glass and a normal viscous metamorphosis. They induced normal clot retraction and permitted normal thromboplastin generation.

Both his intrinsic and extrinsic blood clotting systems were completely normal. His plasma fibrinogen was well within normal range and no increased fibrinolysis could be detected.

Because of a normal tourniquet test and normal appearance of the vessels by capillary microscopy, the possibility of a vascular disturbance is unlikely although not ruled out.

Von Willebrand's disease was ruled out because the levels of antihemophilic A and B factors (factors VIII and IX) were normal, the family history negative and the bleeding tendency probably acquired.

The work of N i l s s o n et al. strongly indicates the existence of a plasma factor necessary for the control of the bleeding time. As 3 l of fresh blood had no shortening effect on the bleeding time, the platelet count remaining unchanged, it does not seem likely that the patient was lacking such a plasma factor. No evidence of a circulating inhibitor of this or other hemostatic factors was obtained in either of the two transfusion experiments.

The case is reported because it suggests the existence of a hemorrhagic diathesis not previously described.

Summary

1) A case of a severe, acquired hemorrhagic diathesis, complicating a carcinoma of the stomach, is reported.

2) The only pathological hemostatic finding was a markedly prolonged bleeding time.

3) Platelets were normal; the capillaries seemed to be normal. There was no increased fibrinolysis, and no other defect in his clotting mechanism could be discovered.

4) The prolonged bleeding time was probably caused by a hitherto undescribed mechanism.

Résumé

1. Une diathèse hémorragique acquise sévère chez un homme de 60 ans avec carcinome de l'estomac est décrite.

2. Le temps de saignement fortement prolongé était le seul défaut de l'hémostase reconnaisable.

3. Les plaquettes étaient normales; la fonction capillaire paraissait normale. La fibrinolyse n'était pas augmentée et aucun autre défaut de la coagulation ne pouvait être reconnu.

4. La prolongation du temps de saignement était probablement due en un mécanisme inconnu jusqu'à présent.

Zusammenfassung

1. Es wird über einen Fall einer schweren, erworbenen hämorrhagischen Diathese, kompliziert durch ein Magenkarzinom, berichtet.

2. Der einzige pathologische Befund bei der Untersuchung des Blutstillungsmechanismus war eine verlängerte Blutungszeit.

3. Thrombozyten und Kapillaren waren normal. Es fand sich keine gesteigerte Fibrinolyse. Es konnte keine andere Störung des Gerinnungsmechanismus gefunden werden.

4. Die verlängerte Blutungszeit war wahrscheinlich durch einen bisher nicht bekannten Mechanismus bedingt.

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