

Thrombocytopenic Purpura as a Probable Manifestation of Insulin Allergy

Report of a Case

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Purpura in diabetes has been rarely described. Joslin and co-workers¹ quote two cases without discussing the relationship between diabetes and the blood changes. Kern and Langer² report nonthrombocytopenic purpura as an allergic manifestation to insulin and Travia³ mentions purpura as a manifestation of allergy to insulin therapy.

The observation of a diabetic patient developing severe thrombocytopenic purpura, the probable connection of the latter with insulin, its favorable reaction to ACTH, prednisone and cortisone therapy, and the important value of in vitro tests to recognize allergens, seem of general interest and to justify publication.

CASE REPORT

A 60-year-old foreman was admitted to the Bethanien hospital May 21, 1955, on account of thrombocytopenic purpura and diabetes mellitus.

His family history was irrelevant, except that, 25 years previously, his only son had died at the age of 7 of aplastic anemia.

Twenty years before the present admission, diabetes was discovered and carefully treated by diet alone until 15 years later, when coronary thrombosis lowered the tolerance and insulin therapy had to be instituted. After improvement of his cardiac function, the patient's condition remained very satisfactory with about 20 units of protamine zinc insulin once daily. However, in April 1955, epistaxis developed, gradually becoming more frequent and severe. On May 20th he consulted his family physician,† who made the diagnosis of thrombocytopenic purpura and referred the patient for hospital treatment.

On admission the patient showed an enormous number of small punctate hemorrhages all over the skin, many small hematomas in his gums, throat, palate and tongue. Neither liver nor spleen was enlarged. Blood pressure was 175/80 mm. Hg. Urine contained 42 gm. of glucose in 24 hours, a trace of acetone, a trace of protein; urobilinogen and urobilin were increased. Capillary blood sugar was 305 mg. per cent; hemoglobin, erythrocytes, leucocytes, differential count normal; thrombocytes numbered 27,000 (Fonio's and Babnik's methods), bleeding time was 8½ min., coagulation time 2½ min., prothrombin time 20 sec.; the nonprotein nitrogen 30 mg. per cent.

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The bone marrow was, according to Dr. Karl Rohr‡ rather rich in fat, erythroblasts about normal in number with mitotic figures; granulopoiesis was normal; megakaryocytes were not decreased, showing basophilia of their cytoplasm and rather young nuclei; there was an increase of plasma cells and reticular elements. The hematologist's conclusion from the increase in plasma and reticular cells and the normal number of megakaryocytes was the presence of a "toxic-allergic" condition.

In order to obtain rapid control of the diabetes, *regular insulin* was substituted for *protamine zinc insulin*. To check the thrombocytopenia, *cortisone* therapy was started immediately after hospital admission. The different drugs used and the most important blood tests are recorded in table 1. The patient's condition improved rapidly. Temperature ranged between 36.4° C on admission and 37° C for the first 12 days, and between 35.8° C and 36.6° C until the 18th day.

Since he had been using protamine zinc insulin for five years without any difficulty and since he had changed neither type nor brand of insulin, it appeared at first very unlikely that insulin could cause the thrombocytopenia. We searched for other substances with benzol-like action, but could not discover any contact with other drugs or related chemical compounds.

Preparing the patient for dismissal from hospital, he was changed from regular to *zinc insulin Semilente*, and on the 18th hospital day, one injection of 26 units was given before breakfast. In the evening the temperature rose to 37.9° C, the platelets had dropped from 60,000 to 40,000, and the patient started to bleed again. This clinical observation roused the suspicion that zinc insulin Semilente might have caused the recurrence. This opinion was fostered when we learned on the same day, that nephelometric examination of the patient's serum when tested with all medications he had received prior to the appearance of thrombocytopenia, showed positive reaction with protamine zinc insulin and with zinc insulin Semilente. That evening *regular insulin* NOVO was used again, but in spite of it, the patient's condition grew rapidly worse. The following morning his temperature rose to 39.7° C, the bleeding from his nose became extremely difficult to control. After 48 hours regular insulin NOVO was re-

THROMBOCYTOPENIC PURPURA AS A PROBABLE MANIFESTATION OF INSULIN ALLERGY

TABLE 1

Date 1955	Insulin	Dosage			Platelets	Cortisone mg.	Prednisone mg.	ACTH units	Penicillin units	Antistin
		morning	noon	evening						
5/21	regular insulin Novo		10	8	22,000	50				300 mg.
5/22	" " "	26	16	30		200				
5/23	" " "	36	16	34	26,000	200				
5/24	" " "	34	16	36		150		300,000		
5/25	" " "	34	20	36	49,000	150		600,000		
5/26	" " "	34	20	24		100		600,000		
5/27	" " "	30	20	26	56,000	100				
5/28	" " "	40	20	26		100				
5/29	" " "	36	20	20		100				
5/30	" " "	36	16	20		100				
5/31	" " "	26	16	20		75				
6/1	" " "	30	16	30	40,000	75				200 mg.
6/2	" " "	36	16	26		50				200 mg.
6/3	" " "	30	20	16		100				200 mg.
6/4	" " "	24	14	14		75				200 mg.
6/5	" " "	30	14	16		100				300 mg.
6/6	" " "	26	16	10	60,000	100				300 mg.
6/7	insulin Novo Semilente	26			40,000	100		600,000		
6/8	regular insulin Novo	8	4	18	45,000	150		300,000		300 mg.
6/9	" " "	20	12			200		340,000		
6/9	regular insulin Wellcome			16	34,000					
6/10	" " "	20	16		20,000	200		600,000		
6/11	regular insulin Novo	0	0	24	10,000, 7,000		40	600,000		200 mg.
6/12	" " "	16	20	20	15,000					
6/13	" " "	12	10	20	14,000	10	164	240,000		
6/14	" " "	16	20	28	10,000, 16,000	15	84	480,000		
6/15	" " "	30	20	34	22,000	30	56	480,000		
6/16	" " "	28	20	16	42,000	30	80	480,000		
6/17	" " "	26	18	16	54,000	30	40	480,000		
6/18	" " "	16	10	10	56,000	30		420,000		
6/19	" " "	10	6	8		15				
6/20	" " "	10	6	6	73,000	15				
6/21	" " "	10	10	8	210,000	5				
6/22	" " "	10	10	8						
6/23	" " "	12	10	8	114,000	20		300,000		
6/24	" " "	12	10	8	60,000	40		300,000		
6/25	" " "	30	16	16	54,000, 60,000	40		300,000		
6/26	" " "	26	16	20		100				
6/27	" " "	28	16	18	70,000	75				
6/28	" " "	26	16	14	83,000	75				
6/29	" " "	28	14	14	76,000	75				
6/30	" " "	22	22	16						
7/1	" " "	16	10		45,000					
7/2	" " "	12	12	10	45,000	125				
7/4	" " "	24	14	16	115,000	125				
7/7	" " "	20	12	10	120,000	100				
7/11	" " "	20	12	10	135,000	75				
7/25	" " "	16	12	8	120,000	75				
8/22	" " "	14	5	8	145,000	25				
9/22	" " "	16	6	8	135,000	37				
10/10	" " "	16	6	8	140,000					
12/11	" " "	16	8	10	140,000					
1/30/56	" " "	20	10	10	180,000					

placed for 24 hours by *regular insulin (Wellcome)*, then for one day *all insulin was withheld*. These changes plus one transfusion of 250 ml. of fresh whole blood did not help. The patient deteriorated rapidly, his thrombocytes dropped to 9,000 and he started to expectorate and to vomit blood.

At this stage intravenous ACTH therapy was started and continued for six and a half days. Prednisone was

given concurrently and for 14 days in varying dosage. The bleeding stopped promptly, but the patient developed a full-moon face, edema and dyspnea. On substituting cortisone for prednisone and ACTH, the retained water was lost rapidly. The general condition of the patient improved so much that he could leave the hospital 12 days after the cessation of ACTH infusions. For almost two months he continued to take

cortisone at home in gradually diminishing dosage, then stopped this therapy, and has continued to use regular insulin and dietary control. The patient is now working normally and feeling fine.

Through the courtesy of Dr. K. Hallas-Møller and J. Schlichtkrull from the Novo Terapeutisk Laboratory in Copenhagen it was possible for Dr. Hoigné* to test the patient's serum with protamine zinc insulin NOVO, zinc insulin NOVO Semilente, insulin NOVO pig glands, zinc insulin NOVO Lente, protamine sulfate, methylparahydroxybenzoate, regular insulin NOVO, crystallized insulin NOVO, insulin NOVO ox glands and procaine. For the detection of the causative allergen, two "in vitro" methods have been used, the "thrombocyte-agglutination test" of Hoigné and Storck⁴ and the nephelometric serological method of Hoigné, Grossmann and Storck.⁵ Both tests gave a positive result with protamine zinc insulin, insulin Semilente, insulin Lente, insulin NOVO pig glands, protamine sulfate and methylparahydroxybenzoate, a negative result with regular insulin NOVO, crystallized insulin NOVO, insulin NOVO ox glands and procaine. The thrombocyte-Coombs test according to the method of Flückiger, Hässig and Koller⁷ and kindly performed by Dr. Flückiger† was negative.

SUMMARY

A diabetic subject is described who, after using protamine zinc insulin for five years, suddenly developed severe thrombocytopenic purpura. Cortisone therapy stopped the bleeding and improved the patient's condition. Following a single dose of zinc insulin Semilente there was a severe recurrence of the purpura with almost fatal outcome. Immediate treatment with ACTH followed by cortisone therapy and avoidance of "in vitro" positive insulins was followed by recovery. The thrombocytopenic purpura in this instance is regarded as an allergic manifestation due to protamine zinc insulin and to zinc insulin, Semilente. "In vitro" tests for the identification of the allergen were positive with

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the same preparations and support the conclusion that the sudden drop in blood-platelet was due to protamine zinc insulin and insulin Semilente.

SUMMARIO IN INTERLINGUA

Purpura Thrombocytopenic Como Manifestation Probabile de Allergia a Insulina

Es describe un subjecto qui, post haber usate insulina a protamina e zinc durante cinque annos, disveloppava subitaneemente sever purpura thrombocytopenic. Therapia a cortisona arrestava le sanguination e meliorava le condition del patiente. Post un sol dose de insulina Semilente a zinc il habeva un sever recurrentia del purpura con exito quasi mortal. Un immediate tractamento con ACTH sequite per therapia a cortisona e le exclusion de insulinas con reacciones positive in vitro resultava in recovramento. Le purpura thrombocytopenic in iste caso es considerate como un manifestation allergic debite a insulina a protamina e zinc e a insulina Semilente a zinc. Tests in vitro pro le identification del allergeno esseva positive con le mesme preparatos lo que supporta le conclusion que le subitane reduction del plachettas sanguinee esseva causate per insulina a protamina e zinc e per insulina Semilente.

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