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Abstract

The female patient initially showed the acquired type of total lipoatrophy at about 8 years of age. At 12 years of age, the onset of diabetes mellitus was speculated from advanced pyodermia and dedentition. At 29 years of age, glucosuria was found, and she developed proteinuria, ascites, and pretibial edema. The physical examination revealed: hepatosplenomegaly, complete absence of subcutanous fat, cutaneous xanthomas, and emaciated facies with pronounced zygomatic arches. Diabetic retinopathy was revealed in the ophthalmological examination, and nephropathy was evident in renal biopsy specimens. She also had peripheral diabetic neuropathy. No adipose tissue was found in the mesenterium under peritoneoscopy. The hepatic biopsy specimen revealed advanced portal liver cirrhosis. Laboratory findings included: hyperlipidemia, elevation of BMR without evidence of hyperthyroidism, impaired renal function, and undetected anti-insulin antibodies and anti-insulin antibodies. Endocrinological examinations revealed normal value, except for an impaired hGH response in the arginine test. C-peptide immunoreactivity was high. Her condition was fairly well controlled by 140 units of insulin injection daily.

KEYWORDS: lipoatrophic diabetes, diabetic triopathy, hepatosplenomegaly, anti-insulin receptor antibodies, CPR

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LIPOATROPHIC DIABETES REPORT OF A CASE

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Key words: lipoatrophic diabetes, diabetic triopathy, hepatosplenomegaly, anti-insulin receptor antibodies, CPR

Lipoatrophic diabetes was first described in 1946 by Lawrence (1). This syndrome was defined by the following characteristics; (a) complete absence of subcutaneous and intra-abdominal fat; (b) insulin-resistant diabetes with little tendency to develop ketosis; (c) hepatosplenomegaly; (d) hyperlipemia with cutaneous xanthoma; and (e) marked elevation of BMR without evidence of hyperthyroidism. After this initial report, other cases were found and much discussion followed on the mechanism and patho-etiology. In Japan, more than 10 lipoatrophic diabetes cases were reported, and several attempts were made to examine the "diabetogenic peptide" characteristics. We describe here a patient with all major characteristics of lipoatrophic diabetes simultaneously with diabetic complications.

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CASE REPORT

The patient was a 32-year-old Japanese female, who had no diabetic or parental consanguinity in her family. Her birth was full term, without noticeable abnormality. At 8 years of age, she gradually became emaciated. At 12 years of age, she began to show dedentition due to alveolar pyorrhea. At the same time, pyodermia was evident in the abdominal wall and buttocks. There was no evidence of polyphagia, polydipsia, and polyuria until she was 29 years of age, when glucosuria was found. Diabetes mellitus was diagnosed, and she was treated with tolbutamide. At 31 years of age, she developed proteinuria, hypertension, and pretibial edema. Several months later, ascites and increased pretibial

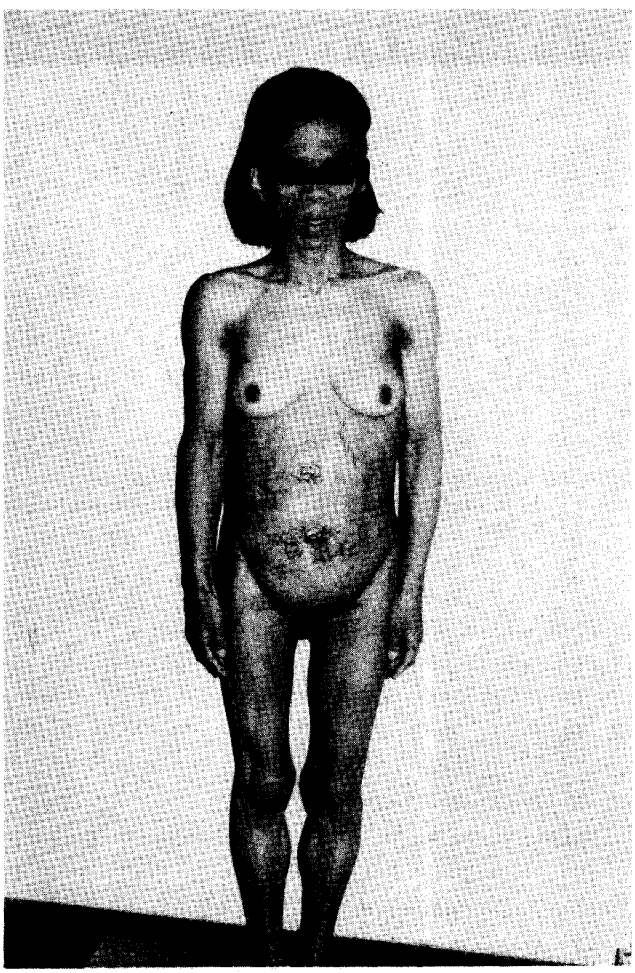

Fig. 1. Photograph of patient at 31 years of age.

Sarai et al.: Lipoatrophic diabetes. Report of a case

edema, hepatosplenomegaly, and cardiomegaly were noted. Her diabetic state was difficult to control by insulin. At this point, she was referred to us for consultation.

Physical examination on admission. The patient was 143 cm tall and weighed 41 kg. Her blood pressure was 140/88 mmHg. She had emaciated facies with pronounced zygomatic arches and was lacking subcutaneous adipose tissue, except for the breast (Fig. 1). The musculatures were prominent. Numerous, widespread cicatrical keroids were observed on the abdominal wall and hip regions. She had hyperpigmented skin and acanthosis nigricans was present in the axillae. Her hair was curly enough but scanty in the axillary and public areas. Xanthomas were evident on the left upper eyelid and in the posterior cervical region. The parotid glands were not enlarged. Almost complete dedentition resulted from alveolar pyorrhea. The liver edge was felt 3 cm below the right costal margin. The spleen was felt 2 cm below the left costal margin. Genitalia was almost normal, except for mild enlargement of the clitoris. In the lower extremities, reflexes were absent, and marked phlebomegaly was present.

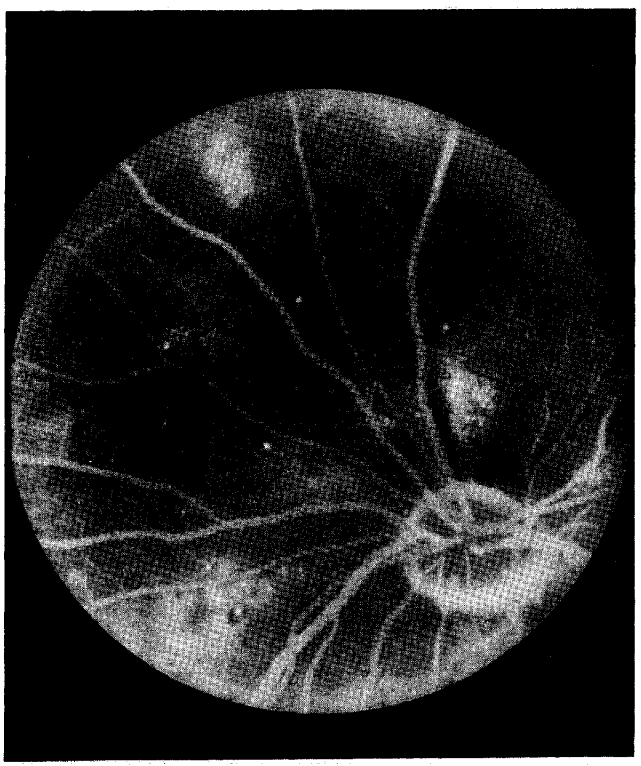

Fig. 2. Fluorescent funduscopy. Numerable microaneurysmas and leakages are seen.

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On funduscopy, the disk appeared normal, but the retina showed marked changes with cotton-wool patches and had hemorrhages. By fluorescent funduscopy, numerable microaneurysmas and leakages were present bilaterally (Fig. 2).

On peritoneoscopy, no adipose tissue was found in the mesenterium and greater omentum. The liver was cirrhotic, and venous dilatation was seen in the portal vein system.

Roentgenograms. Chest x-ray film showed the prominence of the left ventricle. On x-ray films of the skull, the sella turcica was normal in shape and size. X-ray films of the bilateral arms showed marked calcification in the osseous cortices. Pelvic films showed calcification of the femoral arteries.

Biopsy specimens. Diabetic glomerulosclerosis was seen on kidney tissue obtained by percutaneous needle biopsy. Fluorescent antibody technique on the kidney revealed linear staining along the glomerular basement membrane with FITC labelled anti-IgG serum (Fig. 3). Skin biopsy revealed an absence of subcutaneous fat. The hepatic biopsy specimen revealed advanced portal liver cirrhosis (Fig. 4).

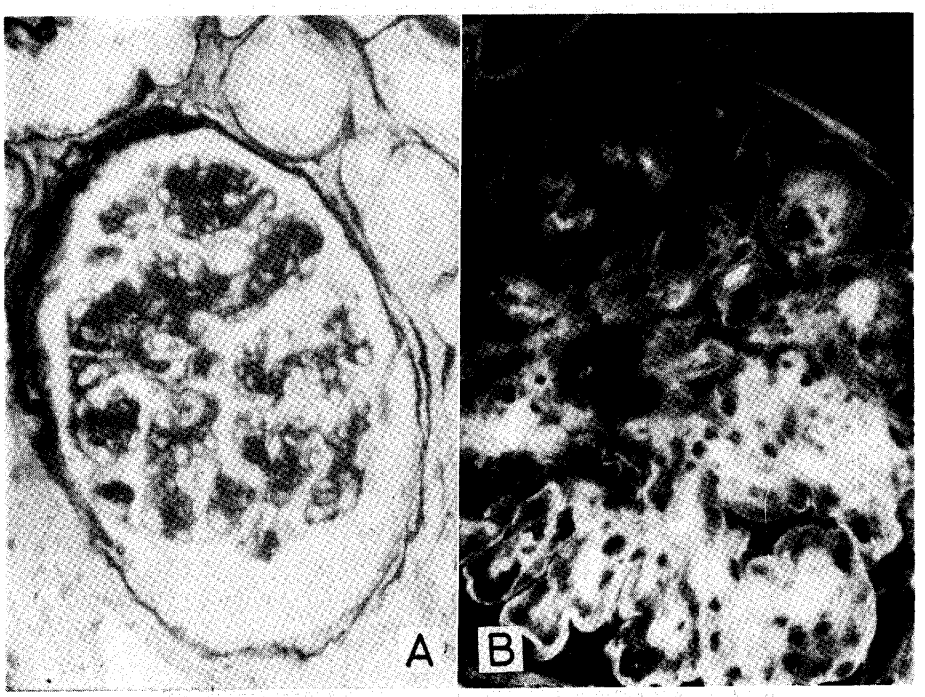

Fig. 3. A. Diabetic glomerulosclerosis. PAS stain, ×400.
B. Linear staining along the glomerular basement membrane with FITC labelled anti-IgG serum.

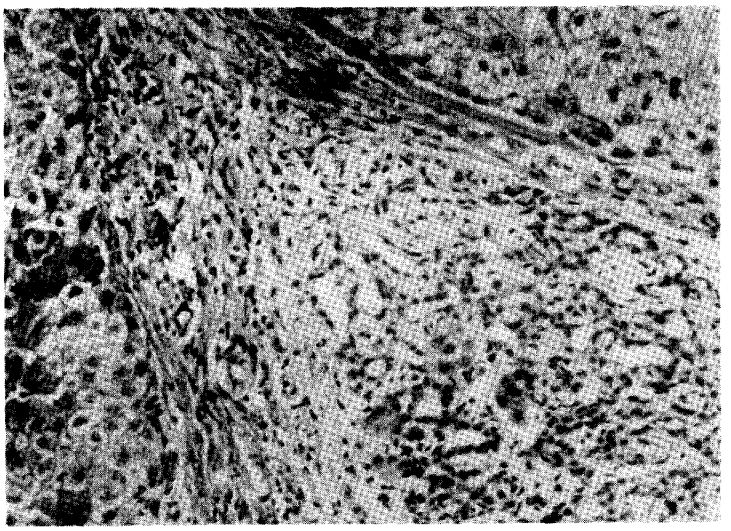

Fig. 4. Advance changes in portal liver cirrhosis. HE stain ×400.

Laboratory findings. Serum electrolytes, blood urea nitrogen, serum creatinine, and the blood picture were within normal limits. The 24-h urinary excretion of glucose ranged from 10 to 20 g and protein from 0.5 to 1.5 g. Total serum protein was 7.4 g/dl, and the electrophoretic pattern showed: albumin 47.1%, alpha$_1$-globulin 2.9%, alpha$_2$-globulin 11.5%, beta-globulin 17.3%, and gamma-globulin 21.2%. Liver function test indicated: serum GOT, 41 u; serum GPT, 65 u; serum Al-p, 4.0 B.L.u; and 25.8% indocyanine green retention in 15 min. Serum lipid values were: NEFA, 720 μEq/l; phospholipid, 244 mg/dl; triglyceride, 196 mg/dl; and total cholesterol, 275 mg/dl. The creatinine clearance was 65.1 ml/min. PSP test showed 37.5% excretion in 30 min, 39.8% in 60 min, and 43.5% in 120 min.

In serological tests, anti-insulin antibodies were negative, and anti-insulin receptor antibodies (kindly assayed by Dr. J.S. Flier of NIH, USA) were not detected. Serologic tests for syphilis were negative; RA tests were negative; anti-nuclear antibodies were negative; anti-thyroglobulin antibodies were negative; and serum complement titer (CH50) was 44 (normal). Immunoglobulin values were: IgG, 1400 mg/dl; IgA, 650 mg/dl; and IgM, 200 mg/dl.

The electroencephalogram was interpreted within normal limits. The intelligence test revealed mild mental retardation. Cerebrospinal fluid on lumbar puncture revealed no abnormality, except for high glucose level.

Thyroid function studies showed: BMR, +35%; T_3-resin sponge uptake, 23%; and T_4 (total), 5.0 μg/dl. In examination of the hypophysio-adrenocortical axis, the LH-RH test and TRH test were within normal. Human growth

hormone (hGH) revealed a hyperresponse to insulin, and no response to arginine (Table 1).

TABLE 1. PATIENT DATA ON ENDOCRINOLOGICAL PARAMETERS

Plasma cortisol

Diurnal variation

Time	μg/dl
9 am	8.0
4 pm	7.2
11 pm	7.5

Overnight dexamethasone suppression test (dexamethasone 1 mg orally)

Time	μg/dl
Initial	8.0
Terminal	1.25

ACTH test
(0.4 mg synthetic ACTH)

Minutes	μg/dl
0	1.25
30	10.0
60	13.8

LH-RH test (0.1 mg LH-RH iv)

Minutes	LH (mIU/ml)	FSH (mIU/ml)
0	12.0	22.8
15	25.0	26.0
30	37.5	27.0
60	32.9	27.0
90	29.0	30.0

Urine 17 KS 10.10 mg/day

Urine 17 OHCS 5.72 mg/day

Growth hormone

Insulin test (0.1 U/kg iv)

Minutes	ng/ml
0	4.7
30	80
60	13.0
90	7.8

Arginine test
0.5 g/kg 30 min iv infusion)

Minutes	ng/ml
0	3.9
30	2.6
60	3.9
120	2.4

TRH test (0.5 mg TRH iv)

Minutes	*TSH* μU/ml
0	4.2
15	10.5
30	12.5
45	15.0
60	15.5
90	11.0
120	9.0

Blood glucose and C-peptide immunoreactivity (CPR) levels during 50 g GTT are shown in Fig. 5. A diabetic pattern was evident, and the CPR level revealed a high basal value. In the tolbutamide test (Fig. 6), CPR showed a good response with high basal value, but blood glucose showed a delayed response. In the arginine test (Fig. 7), CPR level was well correlated to the blood glucose level. The blood glucose concentrations following intravenous administration of

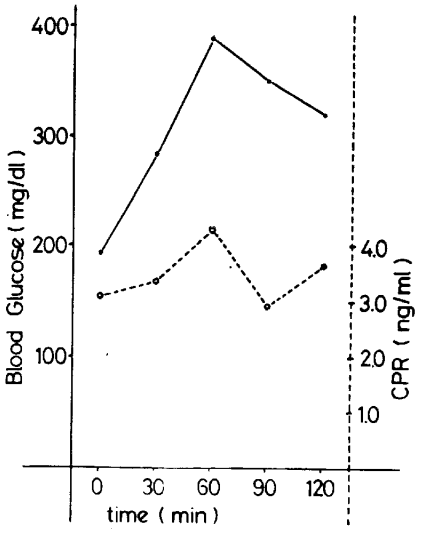

Fig. 5

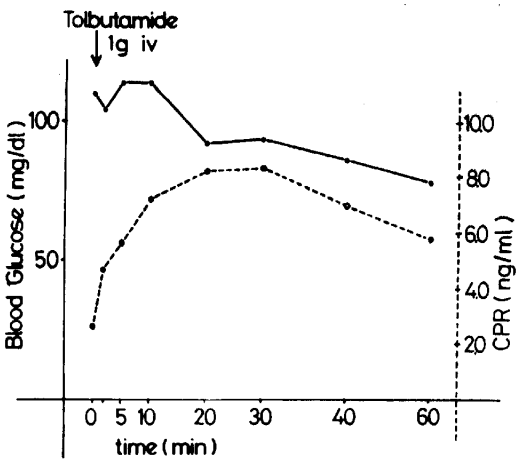

Fig. 6.

Fig. 5. Blood glucose (solid line) and C-peptide immunoreactivity (CPR) (broken line) levels during 50 g GTT. Blood glucose values showed a diabetic pattern, and high CPR level was observed.

Fig. 6. Blood glucose (solid line) and C-peptide immunoreactivity (CPR) (broken line) levels after intravenous injection of 1 g tolbutamide. Tolbutamide evocked a high CPR level and delayed lowering of blood glucose level.

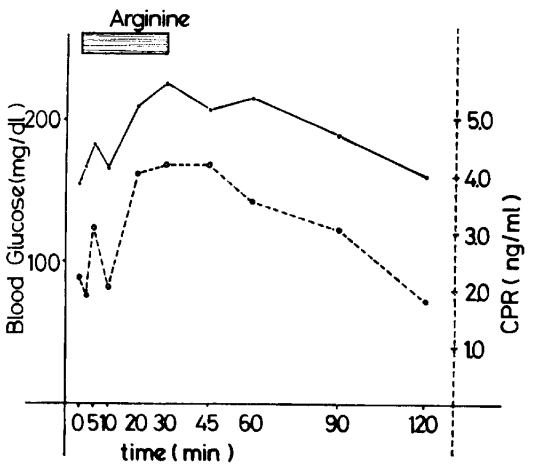

Fig. 7. Blood glucose (solid line) and C-peptide immunoreactivity (CPR) (broken line) levels during arginine (0.5 g/kg) infusion. The CPR level was well correlated to the blood glucose level.

regular insulin (1 unit/kg) were: 272 mg/dl at 0 min, 172 mg/dl at 30 min, 122 mg/dl at 60 min, 110 mg/dl at 90 min, and 106 mg/dl at 120 min. Post-heparin lipolytic activity was markedly decreased: below 0.01 μEq FFA/ml/min at 10, 20 and 30 min.

Clinical course. The patient was fed 1,200 calories (180 g carbohydrate, 60 g protein, 30 g fat) daily after admission. On admission, fasting blood glucose (FBG) was 240 mg/dl and the 24 h urinary glucose was 10 g; then 12 units NPH insulin was administered for 60 days. In the meantime, the patient had an episode of urinary tract infection due to atonic bladder. Cephalexin at 1 g daily was administered, but an adverse reaction appeared in the liver. In spite of improvement in serum GOT, GPT, and Al-p levels, severe glucose intolerance was found. Though NPH insulin was increased to 100 units daily, FBG was still about 300 mg/dl, and the 24 h urinary glucose output was about 50 g. After increasing NPH insulin to 140 units daily, she showed fairly good control of FBG decreasing to about 170 mg/dl. Pimozide administration was attempted for 40 days starting with an initial dose of 1 mg daily and ending with 4 mg daily. No effect was obvious on the symptoms. She experienced recurrent exacerbation of chronic pyodermia and chronic cystitis throughout her hospitalization period.

DISCUSSION

This patient had all the characteristics of acquired lipoatrophic diabetes. The lipodystrophy might have occurred at 8 years of age, followed later by the onset of diabetes mellitus that was suspected by the advanced dedentition and pyodermia. This patient was referred to us as insulin resistant diabetes, but on admission, the condition was fairly well controlled by 12 units NPH insulin and diet control. She developed severe glucose intolerance after an episode of liver injury. After increasing the dose of insulin to 140 units daily, the diabetes was again fairly well controlled. The patient also had retinopathy, neuropathy, and nephropathy as complications. Many investigators have reported the tendency for diabetic complications, especially in a poorly control situation (2). Podolsky (3) reported 1/ nephropathy cases out of 64 cases with lipoatrophic diabetes. Sato and his colleagues (4) reported three retinopathy out of five lipoatrophic diabetes cases.

Many recent reports have related the pathogenesis of lipoatrophic diabetes to hypothalamic derangement. Seip (5) reported a widening of the basal cistern and third ventricle by pneumoencephalography in several patients. In the same report, Seip described the lipid center in the anterio-inferior hypothalamus of dog with hyperlipemia and decreased adipose tissue.

In endocrinological studies, several investigators (6) have reported impaired hGH response in several tests. In our case, tests of the hypophysio-adrenocortical

axis, LH-RH test and TRH tests were within normal limits. The hGH levels indicated a hyperresponse to insulin and no response to arginine.

In 1963 Louis and his colleagues (7) found a peptide of insulin antagonist in the urine of patients with lipoatrophic diabetes. This peptide made dogs insensitive to insulin and intolerant to glucose. They called this peptide diabetogenic peptide which was secreted from the pituitary body and probably had a pathogenetic role in the condition. This substance is difficult to extract and define, and was not always detected in patients. In our study here, we were not able to detect this substance. Pimozide, a cerebral dopaminergic blocking agent, could possibly correct the diencephalon-hypothalamic abnormality. In 1974, Corbin *et al.* (8) reported several lipodystrophy cases improving after pimozide administration. In our case, we could not determine its efficacy.

Kahn *et al.* (9) reported cases with a syndrome of insulin resistance and acanthosis nigricans, and divided these cases into two types: Type A, a syndrome in younger females with signs of virilization or accelerated growth, in whom the receptor defect might be primary, and Type B, a syndrome in older females with signs of an immunologic disease, in whom circulating antibodies to insulin receptor were found. In Type A patients many features were similar to those in lipoatrophic diabetes. However, Type A patients did not have lipoatrophy, hyperlipidemia, or hepatomegaly. Oseid and his colleagues (10) reported four cases with congenital generalized lipodystrophy with extreme insulin resistance. In their patients, mononuclear leukocytes bound significantly less insulin than normal subjects after 12 h of fasting. After 60 h of fasting, insulin binding increased, and this rise was followed by decreased plasma insulin level. These phenomena suggest a possible reversal of the receptor defect, which argues against a primary receptor defect and indicates changes in receptor number. However, Scatchard analysis suggested a decrease in binding affinity in cells of these patients. These investigators suggested that the interference of receptor antibodies might also be the cause of receptor abnormality in congenital generalized lipodystrophy. Rosenbloom *et al.* (11) tested insulin binding to cultured fibroblasts of lipoatrophic diabetes patients and found that the cells of these patients did not differ significantly on any characteristic from normal control subjects. These findings indicated that a basic defect is not present in insulin receptors of lipoatrophic diabetes. These same investigators mentioned that a secondary disruption of binding, *e.g.*, by a circulating factor remained possible. In our case, the basal CPR level was high, and anti-insulin antibodies and anti-insulin receptor antibodies were not detected. Further investigations on insulin receptor abnormalities in lipoatrophic diabetes will be attempted in the future.

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