Case Report

A Case of Insulin Dependent Diabetes Mellitus Associated with Relapsing Polychondritis, Hashimoto's Thyroiditis and Pituitary Adrenocortical Insufficiency in Succession.

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The case of a 40 year-old woman with insulin dependent diabetes mellitus associated with relapsing polychondritis, Hashimoto's thyroiditis and pituitary adrenocortical insufficiency in succession, considered as polyglandular autoimmune syndrome type III, is described. The results of this study suggest that relapsing polychondritis and pituitary adrenocortical insufficiency might be included in polyglandular autoimmune syndrome. It is very interesting that in the pathogenicity of polyglandular autoimmune syndrome type III, the elevation of OKT4/OKT8 ratio which indicates the hypofunction of suppressor T cell is shown and that she has HLA DR4 which has a significant relationship with insulin dependent diabetes mellitus in Japanese.

Key Words: Insulin dependent DM, Relapsing polychondritis, Hashimoto's thyroiditis, Pituitary adrenocortical insufficiency, Polyglandular autoimmune syndrome type III.

Since Schmidt (1) reported two patients with coexistent non-tuberculous adrenal insufficiency and lymphocytic thyroiditis in 1926, it has been well known that the dysfunction of endocrine glands is based on a mutually associated autoimmune mechanism. Recently, Neufeld et al. (2) proposed to term them polyglandular autoimmune syndrome (PGA syndrome) and to classify them into three groups (type I, type II, type III). However, because PGA syndrome involves not only multiple endocrine organ disorder but several nonendocrine-specific autoimmune disorders, the clinical character of this syndrome is indefinite in its details.

We describe a case of insulin dependent diabetes mellitus (IDDM) associated with relapsing polychondritis (RP), Hashimoto's thyroiditis and pituitary adrenocortical insufficiency in succession, considered as PGA syndrome type III.

REPORT OF A CASE

A 40 year-old woman was admitted to our clinic because of hyperglycemia in October 1984. Seven years before admission, after suffering from rubella, she had easy fatigability and thirst, and was diagnosed as diabetes mellitus by a physician. She received insulin treatment of 45 units per day. A month before admission, she noticed mild dyspnea with hoarseness. Because her dyspnea was prolonged and aggravated, she visited the Otolaryngology Department in Kochi Medical School Hospital and was found to have tracheal stenosis. Subsequently, she received a tracheotomy which relieved her severe dyspnea. Because hyperglycemia persisted, she was referred to our clinic. She had no family history of metabolic or autoimmune disease.

On admission, she was not obese (height 153cm, body weight 44kg) and had normal blood pressure

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(118/78mmHg). The palpebral conjunctiva was slightly anemic and bulbar conjunctiva was hyperemic, which was diagnosed as iritis with scleritis by an ophthalmologist. She had a saddle nose but no auricular deformity, struma, swelling of lymph nodes, heart murmur, nor swelling or deformity in any joints. The fundusscopic examination demonstrated diabetic retinopathies (Scott IIa).

Laboratory data on admission was as follows (Table 1): Erythrocyte sedimentation rate was 60mm/1 hour. Urinalysis showed marked glucosuria but no ketonuria. Blood analysis revealed mild anemia (Hb 10.5g/dl, RBC 366×10⁴/cmm) but normal white blood cell count. Fasting blood glucose level was elevated (299mg/dl) and serum GOT and GPT levels were mildly elevated (44IU/L and 60IU/L, respectively) but serum lipids, electrolytes and immunoglobulin levels were within normal ranges. Serum T3 level was low but serum T4 and TSH levels were within normal ranges. HbA1c level was elevated (9.9%) and C-peptide immunoreactivities in serum and urine were less than measurable levels (0.3ng/ml and 3.9 μg/day, respectively). Serum C-reactive protein was weakly positive and the RA test, the LE test and anti nuclear factor were negative. Both the titers of the thyroid

and the microsome tests were 1:100. Neither islet cell antibody (ICA) nor islet cell surface antibody (ICSA) was detectable. Patient's serum did not react to human type II collagen (Behring, Co. Ltd.) in the Ouchterlony method. Human leucocyte antigens were A24(9), A26(10), BW61(40), B39(16), CW3, CW7, DR4, DRW13(W6). No abnormality was disclosed in the renal function tests, electrocardiogram or chest radiogram. Tracheography demonstrated a narrowing with smooth contour in the subglottis region (Fig. 1). Histopathological examination of biopsy specimen from tracheal cartilage revealed the degeneration and necrosis of cartilage with lymphocytic infiltration by the hematoxylin-eosin stain (Fig. 2). There was a moderate loss in acidic polysaccharide by the alcian-blue stain.

Clinical course during hospitalization is shown Fig. 3. After admission, the diagnosis of IDDM and RP were made on the basis of these data. Treatment was performed mainly for blood glucose regulation. In the course of admission, iritis was lightened but persisted, and the pains of left sternoclavicular and right foot joints, and mild fevers intermittently occurred. Because serum T3 and T4 levels were gradually decreased associated with increases of

Table 1. Laboratory data on admission.

ESR(mm/hr)	60	Proteinogram(serum)	
Urinalysis		TP(g/dl)	6.6
protein	(-)	Alb.(%)	58.0
glucose	(4+)	γ -gl.(%)	17.0
ketone	(-)	IgG(mg/dl)	1240
Peripheral blood		IgA(mg/dl)	365
Hb(g/dl)	10.5	IgM(mg/dl)	130
RBC(x10 ⁴ /mm ³)	366	Thyroid function	
WBC(/mm ³)	4,500	serum T ₃ (ng/dl)	47
Plt.(x10 ⁴ /mm ³)	29.4	serum T ₄ (μg/dl)	6.95
Blood chemistry		TSH(μU/ml)	4.45
FBG(mg/dl)	299	HbA1c(%)	9.9
GOT(IU/l)	44	CPR serum(ng/ml)	<0.3
GPT(IU/l)	60	urine(μg/day)	<3.9
Al-P(IU/l)	178	Serological examination	
LDH(IU/l)	238	CRP	(+)
T-Ch(mg/dl)	186	RA test	(-)
TG(mg/dl)	154	LE test	(-)
Crn(mg/dl)	0.5	anti-nuclear antibody	(-)
BUN(mg/dl)	18	thyroid test	x100
UA(mg/dl)	1.7	microsome test	x100
Na(mEq/l)	134	ICA	(-)
K(mEq/l)	4.3	ICSA	(-)
Cl(mEq/l)	98	anti typeII collagen	(-)
Ca(mEq/l)	4.2	HLA A24(9)A26(10)BW61(40)	
P(mEq/l)	1.8	B39(16)CW3CW7DR4DRW13(W6)

Fig. 1. Tracheography demonstrated a narrowing with smooth contour in subglottis region.

Fig. 2. Light microscopic findings of the biopsy specimen from tracheal cartilage show the degeneration and necrosis of cartilage with lymphocytic infiltration (H-E stain, $\times 100$).

serum TSH levels and the titers of the microsome test (1:100—1:6,400), the association of Hashimoto's thyroiditis was considered. After supplement of levothyroxine Na was begun in May 1986, serum T3 and T4 levels were normalized. Because it was difficult to regulate blood glucose levels, continuous subcutaneous insulin infusion was performed. However, blood glucose levels showed a tendency to be unstable. From January 1986, insulin requirements were gradually decreased to 10 units per day and she was discharged in December 1986.

In January 1987, because easy fatigability and anorexia occurred, a decrease of insulin dose to 4

units per day was indicated. However, on 29th January 1987, her husband noticed that she was comatose and brought her to our clinic. After intravenous glucose administration, she became alert and was readmitted for intensive examination and further therapy.

Laboratory data on readmission was shown in Table 2 and Fig. 4. Fasting blood glucose, serum sodium, serum cortisol and urinary 17-hydroxycorticosteroids (17-OHCS) levels were 42mg/dl, 115mEq/l, 0.4 μ g/dl and 0.5mg/day, respectively. Urinary 17-OHCS levels in ACTH test (intramuscular administration of 0.5mg tetracosactide acetate for three days) rose from less than 1.0mg/day to 7.7mg/day. Both serum luteinizing hormone and follicular stimulating hormone levels showed normal elevation in the luteinizing hormone releasing hormone test and both serum thyroxine stimulating hormone and prolactin levels demonstrated near normal responses in the thyrotropin releasing hormone test. However, serum growth hormone (GH) levels showed low response in the arginine provocative test. Patient's serum was positive for antibody to AtT-20 cells (mouse adrenocorticotrophic hormone secreting cell) by immunofluorescence method (Sohgo Biomedical Laboratories). In the OKT series, OKT3, OKT4 and OKT8 ratios were 46.0%, 35.5% and 11.4%, re-

Fig. 3. Clinical course of this patient. CIT: conventional insulin therapy, CSII: continuous subcutaneous insulin infusion, US: urine sugar.

Fig. 4. Endocrinological examination.

Table 2. Laboratory data on readmission.

FBG(mg/dl)	42	Serological examination	
Urine glucose(mg/dl)	50	CRP	(+)
Urine protein(mg/dl)	5	RA	(-)
Electrolytes		anti-nuclear antibody	(-)
serum Na(mEq/l)	115	anti-DNA	(-)
K (mEq/l)	4.4	thyroid test	<100
Cl(mEq/l)	82	microsome test	X6400
urine Na(mEq/day)	47	TBII	(-)
K (mEq/day)	186	anti-pituitary cell antibody	
Cl(mEq/day)	43	cytoplasm	
Hormonal examination		anterior lobe	(-)
serum		middle lobe	(-)
ACTH(pg/ml)	16	cell membrane	
GH(ng/ml)	1.3	AtT-20 cell	(+)
LH(MIU/ml)	14.2	GH3 cell	(-)
FSH(MIU/ml)	15.3	OKT series	
prolactin(ng/ml)	29.0	OKT3(%)	46
ADH(pg/ml)	4.6	OKT4(%)	35.5
cortisol(μg/dl)	0.4	OKT8(%)	11.4
urine		OKT4/OKT8	3.11
17-OHCS(mg/day)	0.5		
17-KS (mg/day)	0.8		

spectively and OKT4/OKT8 ratio was 3.11. No abnormality was demonstrated in the sella turcica or the hypothalamic region by high resolution computed tomography.

After readmission, anorexia and hyponatremia persisted in spite of the supplement of physiological saline. The association of pituitary adrenocortical insufficiency was considered. After the supplement

of 10mg per day of hydrocortisone was started, her general condition rapidly improved. Serum sodium levels were normalized and insulin requirements were increased to 20 units per day. In May 1987, she was discharged and has continued to feel well as an out-patient.

DISCUSSION

On the basis of sudden onset after suffering rubella and low C-peptide levels in serum and urine, diabetes mellitus in this case is considered as IDDM. And because the onset of IDDM was about seven years ago, the negative findings in ICA and ICSA are regarded as compatible.

The diagnosis of RP has usually been based on the diagnostic criteria which McAdam et al. proposed (3). She had iritis, saddle nose and stenosis in the subglottis region; that is, she had three items of this criteria. On the basis of these findings and histopathological findings of tracheal cartilage, she was diagnosed as RP. In the course of IDDM and RP, hypothyroidism and pituitary adrenocortical insufficiency occurred in succession. In view the high titers in the microsome test, hypothyroidism in this case may be considered as Hashimoto's thyroiditis.

Concerning pituitary adrenocortical insufficiency in this case, because it has been well known that blood glucose and thyroid hormone levels influence the secretion of GH (4), it is indefinite as to whether there was coexistence of insufficient secretion of GH or not, though serum GH levels showed low response in the arginine provocative test. And because corticotropic releasing factor stimulation test was not done, hypothalamic adrenocortical insufficiency was not ruled out in the strict sense. However, it is very interesting that antibodies to AtT-20 cells were positive. Recently, Sugiura et al. (5) reported that among adrenocorticotrophic hormone deficient patients, all sera were positive for antibodies to AtT-20 cells, and suggested the possibility that antibodies to AtT-20 cells may contribute to the pathogenecity of the autoimmune mechanism which causes the adrenocorticotrophic hormone deficiency. Also this case, the possibility that adrenocorticotrophic hormone secreting cells were attacked by means of the autoimmune mechanism (hypophysitis) has been suggested.

Subsequently, we describe the relationship among

IDDM, RP, Hashimoto's thyroiditis and pituitary adrenocortical insufficiency in this case. Neufeld et al. (2) classified PGA syndrome into three types in 1981. In this classification, type I PGA syndrome is present in patients who have at least two of the triad of Addison's disease, hypoparathyroidism and chronic mucocutaneous candidiasis. Type II PGA syndrome is present in patients who have Addison's disease with autoimmune thyroid disease and/or IDDM, but who do not have hypoparathyroidism or candidiasis. Type III PGA syndrome is present in those who have autoimmune thyroid disease, without Addison's disease, but with another autoimmune disease which most frequently involve IDDM and/or pernicious anemia. In addition, it is known that lymphocytic hypophysitis, myasthenia gravis, primary biliary cirrhosis and the collagen disease which involves rheumatoid arthritis and polymyalgia rheumatica-giant cell arteritis, are also included in type III PGA syndrome spectrum (6).

On the basis of having Hashimoto's thyroiditis and IDDM, she may be considered as having PGA syndrome type III in Neufeld's classification. As concerns RP, it has been reported that RP is frequently associated with autoimmune diseases and/or autoimmune thyroiditis in clinical observations (3, 7), that antibodies to type II collagen may contribute to the pathogenicity of RP (8) and that the degeneration and necrosis of cartilage with lymphocytic infiltration is characteristic of RP in histopathological examination (3). These previous reports and the observations in this case suggest that RP be included in PGA syndrome which is characteristic of having organ specific antibodies and organ damage. In addition, on the basis of being positive for anterior pituitary cell surface antibodies, and on previous reports in which lymphocytic hypophysitis which causes the autoimmune mechanism is associated with Hashimoto's thyroiditis (6, 9, 10) and in which all sera were positive for antibodies to AtT-20 cells among adrenocorticotrophic hormone deficient patients (5), pituitary adrenocortical insufficiency in this case is considered as autoimmune hypophysitis and may be included in PGA syndrome.

As concerns the pathogenicity of PGA syndrome, it was reported that type I may be caused by the hypofunction of suppressor T cells and type II may be related to HLA B8(DW3) (2). However, the pathogenicity of type III is unclear. It is very interesting in regard to the pathogenicity of type III that in this case, the elevation of OKT4/OKT8 ratio which indicates hypofunction of suppressor T cell, is shown and she has HLA DR4 which has a significant relationship with IDDM in Japanese (11).

REFERENCES

- 1) Schmidt MB: Eine Biglandulare Erkrankung (Nebennieren und Schilddrüse) bei Morbus Addisoni. *Dtsch Pathol Ges* **21**: 212, 1926.
- 2) Neufeld M, Maclaren NK and Blizzard RM: Two types of autoimmune Addison's disease associated with different polyglandular autoimmune (PGA) syndromes. *Medicine* **60**: 355, 1981.
- 3) McAdam LP, O'Hanlan MA, Bluestone R, et al: Relapsing polychondritis: Prospective study of 23 patients and a review of the literature. *Medicine* **55**: 193, 1976.
- 4) Daughaday WH: The anterior pituitary, *Textbook of endocrinology*, 7th ed. (Wilson JD and Foster DW eds), WB Saunders Company, Philadelphia, 1985, p568.
- 5) Sugiura M, Hashimoto A, Shizawa M, et al: Detection of antibodies to anterior pituitary cell surface membrane with insulin dependent diabetes mellitus and adrenocorticotrophic hormone deficiency. *Diabetes Res* **4**: 63, 1987.
- 6) Leshin M: Southwestern internal medicine conference: Polyglandular autoimmune syndrome. *Am J Med Sci* **290**: 77, 1985.
- 7) Clement JM, McKenna CH, Luthra HS, et al: Relapsing polychondritis. Survival and predictive role of early disease manifestations. *Ann Int Med* **104**: 74, 1986.
- 8) Foidart JM, Abe S, Martin GR, et al: Antibodies to type II collagen in relapsing polychondritis. *N Engl J Med* **299**: 1203, 1978.
- 9) Goudie RB and Pinkerton PH: Anterior hypophysitis and Hashimoto's disease in a young woman. *J Pathol Bacteriol* **83**: 584, 1962.
- 10) Hume R and Roberts GH: Hypophysitis and hypopituitarism: Report of a case. *Br Med J* **2**: 548, 1967.
- 11) Kawa A, Nakazawa S, Kono Y, et al: HLA system in Japanese juvenile diabetes, *Childhood diabetes in Asia*, (Mimura G and Hibi I eds), Medical Journal Sha, Tokyo, 1979, p19.