【 CASE REPORT 】

Dramatic Improvement of Glycemic Control by Promptly Starting Steroid Therapy at an Early Stage of Autoimmune Pancreatitis in a Subject with Type 2 Diabetes

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Abstract:

Glucocorticoid therapy is effective for treating autoimmune pancreatitis, but autoimmune pancreatitis itself and steroid therapy aggravate glycemic control. A 77-year-old man with type 2 diabetes was consulted due to aggravation of glycemic control. He was diagnosed with autoimmune pancreatitis. We promptly started glucocorticoid therapy for autoimmune pancreatitis and insulin therapy for glycemic control. Subsequently, both pancreatitis and diabetes were markedly ameliorated. After stopping glucocorticoid therapy, good glycemic control continued with diet therapy alone. Starting glucocorticoid therapy at an early stage of autoimmune pancreatitis is very important for preserving the insulin secretory capacity and improving glycemic control.

Key words: autoimmune pancreatitis, steroid therapy, insulin secretory capacity

Introduction

Autoimmune pancreatitis, which was first proposed by Yoshida et al. (1) in 1995, is a pancreatic disorder characterized by immunological abnormalities. Two histological subtypes of autoimmune pancreatitis have been recognized, and type 1 autoimmune pancreatitis is regarded as a subtype of Immunoglobulin (Ig)G4-related diseases (2, 3). According to previous reports, approximately 40-80% of autoimmune pancreatitis cases are associated with diabetes mellitus, and approximately 30-40% of autoimmune pancreatitis patients have a history of diabetes treatment (4, 5). Glucocorticoid therapy is considered effective for treating autoimmune pancreatitis, but both autoimmune pancreatitis itself and glucocorticoid therapy are risk factors for aggravating glycemic control (4, 6). Therefore, whether or not glucocorticoid therapy is truly beneficial for the pancreatic function in subjects with autoimmune pancreatitis and diabetes has been controversial.

Case Report

A 77-year-old man with type 2 diabetes (T2DM) consulted our hospital due to elevated HbA1c levels. He had been treated with only diet therapy for T2DM for about 10 years, and there were no remarkable findings on physical or neurological examinations. He had a history of pharyngeal cancer at 61 years of age and prostatitis at 71 years of age but no remarkable family history.

On admission, his height, body weight and body mass index (BMI) were 160.8 cm, 52.8 kg and 20.4 kg/m^2, respectively. His vital signs included a heart rate of 60 beats/min and blood pressure of 96/56 mmHg. He was a smoker but had stopped smoking at 61 years of age, and he was not a drinker. His glycemic control was poor [plasma glucose, 421 mg/dL; hemoglobin A1c (HbA1c), 10.1%; glycoalbumin 45.2%] even after treatment with 50 mg/day of sitagliptin and 10 mg/day of gliclazide.

Table shows the laboratory data for this subject. The renal and liver functions were almost within normal ranges. The

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Table.   Laboratory Data on Admission in This Subject.

Variable	Result	Reference range	Variable	Result	Reference range
Peripheral blood			Dyslipidemia marker		
White blood cells (/μL)	5,580	3,300-8,600	Total cholesterol (mg/dL)	120	142-248
Red blood cells (×10⁴/μL)	304	435-555	LDL cholesterol (mg/dL)	50	65-139
Hemoglobin (g/dL)	10.0	13.7-16.8	HDL cholesterol (mg/dL)	52	40-90
Platelets (×10⁴/μL)	20.0	15.8-34.8	Triglyceride (mg/dL)	59	40-149
Blood biochemistry			Diabetes marker		
Total protein (g/dL)	6.5	6.6-8.1	Plasma glucose (mg/dL)	421	
Albumin (g/dL)	4.0	4.1-5.1	Hemoglobin A1c (%)	10.1	4.9-6.0
Total bilirubin (mg/dL)	2.3	0.4-1.5	Glycoalbumin (%)	45.2	12.4-16.3
AST (U/L)	22	13-30	Insulin (μU/mL)	2.2	0.0-18.0
ALT (U/L)	23	10-42	Pancreatitis marker		
LDH (U/L)	195	124-222	Amylase (U/L)	199	44-132
ALP (U/L)	272	106-322	Pancreatic amylase (U/L)	139	19-53
γ-GTP (U/L)	16	13-64	Lipase (U/L)	275	17-57
BUN (mg/dL)	24	8-20	Trypsin (ng/mL)	1,915	100-550
Creatinine (mg/dL)	1.05	0.65-1.07	Elastase-1 (ng/dL)	674	0-300
Cholinesterase (U/L)	201	240-486	IgG4 (mg/dL)	203	4.5-117.0
CRP (mg/dL)	0.04	<0.14	Urinary test		
Sodium (mmol/L)	133	138-145	Urinary pH	5.0	5.0-7.5
Potassium (mmol/L)	5.5	3.6-4.8	Urinary protein	-	-
Chloride (mmol/L)	100	101-108	Urinary sugar	3+	-
			Urinary ketone body	-	-

AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, γ-GTP: γ-glutamyltranspeptidase, BUN: blood urea nitrogen, CRP: C-reactive protein, IgG4: immunoglobulin G4

fasting laboratory data were as follows: plasma blood glucose, 261 mg/dL; plasma insulin, 2.2 μU/mL; C-peptide immunoreactivity (CPR), 1.7 ng/mL; CPR index (CPI), 0.65, and urinary CPR excretion, 16.0 μg/day. Anti-glutamic acid decarboxylase (GAD) antibody was negative. The pancreatitis-associated data were as follows: amylase, 199 U/L; pancreatic amylase, 139 U/L; lipase, 275 U/L; trypsin, 1,915 ng/mL; elastase-1,674 ng/dL. The tumor marker data were as follows: carcinoembryonic antigen, 6.0 ng/mL; carbohydrate antigen 19-9, <5.0 U/mL; prostate-specific antigen, 0.983 ng/mL; DUPAN-2, 430 U/mL; Span-1, 10 U/mL. Ig G4 levels were elevated to 203 mg/dL, but other immunoglobulin levels were within normal ranges (IgG 1,220 mg/dL, IgA 200 mg/dL, IgM 132 mg/dL). No other autoimmune diseases were suggested (anti-nuclear antibody <5.0 (-), SS-A/Ro antibodies <1.0 U/mL, SS-B/La antibodies <1.0 U/mL, myeloperoxidase (MPO)-anti-neutrophil cytoplasmic antibody <1.0 U/mL, proteinase-anti-neutrophil cytoplasmic antibody (PR3-ANCA) <1.0 U/mL).

We performed abdominal ultrasonography to examine the cause of the aggravation of his T2DM and exclude the possible presence of malignant disease. Abdominal ultrasonography showed a low-echoic 4×20-mm tumor in the pancreatic body. The main pancreatic duct was interrupted by the tumor, and the peripheral main pancreatic duct was enlarged to 5.4 mm. Dynamic abdominal computed tomography (CT) (Fig. 1) and magnetic resonance imaging revealed irregular narrowing and enlargement of the main pancreatic duct and a low-density area in the pancreatic body,

showing low intensity in the early phase and enhancement in the late phase. Such irregular narrowing of the main pancreatic duct was more clearly observed on endoscopic retrograde cholangiopancreatography (Fig. 2). Immunohistochemical staining of the biopsy species from the pancreas revealed abundant IgG4-positive plasma cell infiltration, with over 40% of the observed area occupied by such infiltration (Fig. 2). Based on such findings, we finally diagnosed him with autoimmune pancreatitis.

Since glucocorticoid therapy is known to be effective in cases of autoimmune pancreatitis, we started 30 mg/day of prednisolone. The pancreatitis markers and IgG4 levels subsequently decreased. We tapered the prednisolone dose and finally stopped steroid therapy altogether about four months later (Fig. 3). His glycemic control was aggravated when he was diagnosed with autoimmune pancreatitis. We therefore increased the insulin dose just after the administration of glucocorticoid therapy. About four months later, we also stopped the insulin therapy and continued with diet therapy. Fortunately, even after stopping insulin therapy, good glycemic control was maintained, and his insulin secretory capacity was preserved (plasma blood glucose: 128 mg/dL, plasma insulin: 3.8 μU/mL, CPR: 1.6 ng/mL, CPI: 1.25). His good glycemic control continued, and the HbA1c levels remained under 7% for over 6 months with only diet therapy.

Abdominal computed tomography (5 months before)

Enhanced abdominal computed tomography

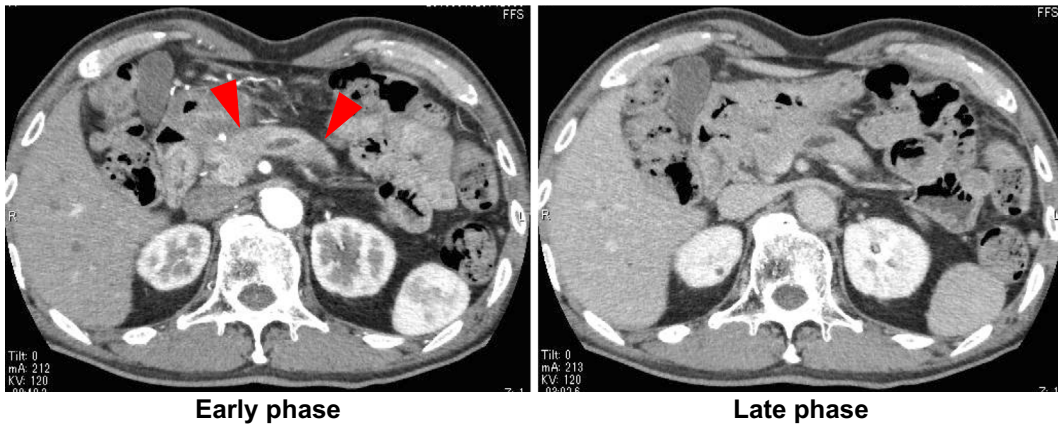**Early phase**　　　　　　　　　　　**Late phase**

Figure 1. Abdominal computed tomography obtained five months before the patient's presentation showed a normal pancreas. Enhanced abdominal computed tomography showed irregular narrowing and enlargement of the main pancreatic duct and a low-density area (red triangle) in the pancreatic body, which showed low intensity in the early phase and enhancement in the late phase.
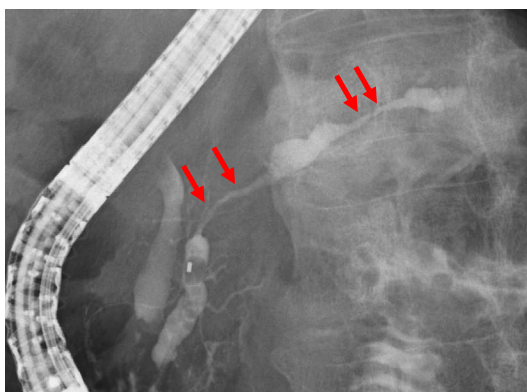
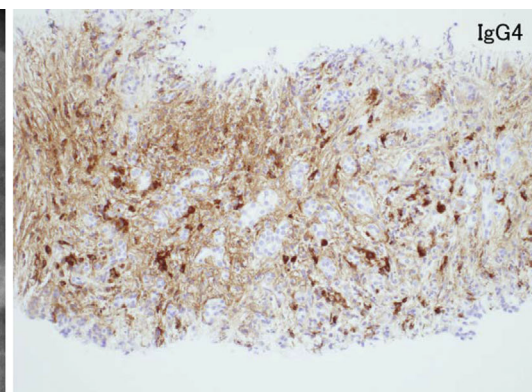**Endoscopic retrograde cholangiopancreatography**　　　　　**Immunohistochemical staining**

Figure 2. Endoscopic retrograde cholangiopancreatography showed the irregular narrowing (red arrow) and enlargement of the main pancreatic duct. Immunohistochemical staining of the biopsy specimens from the pancreas revealed abundant IgG4-positive plasma cell infiltration, with over 40% of the observed area occupied by such infiltration.
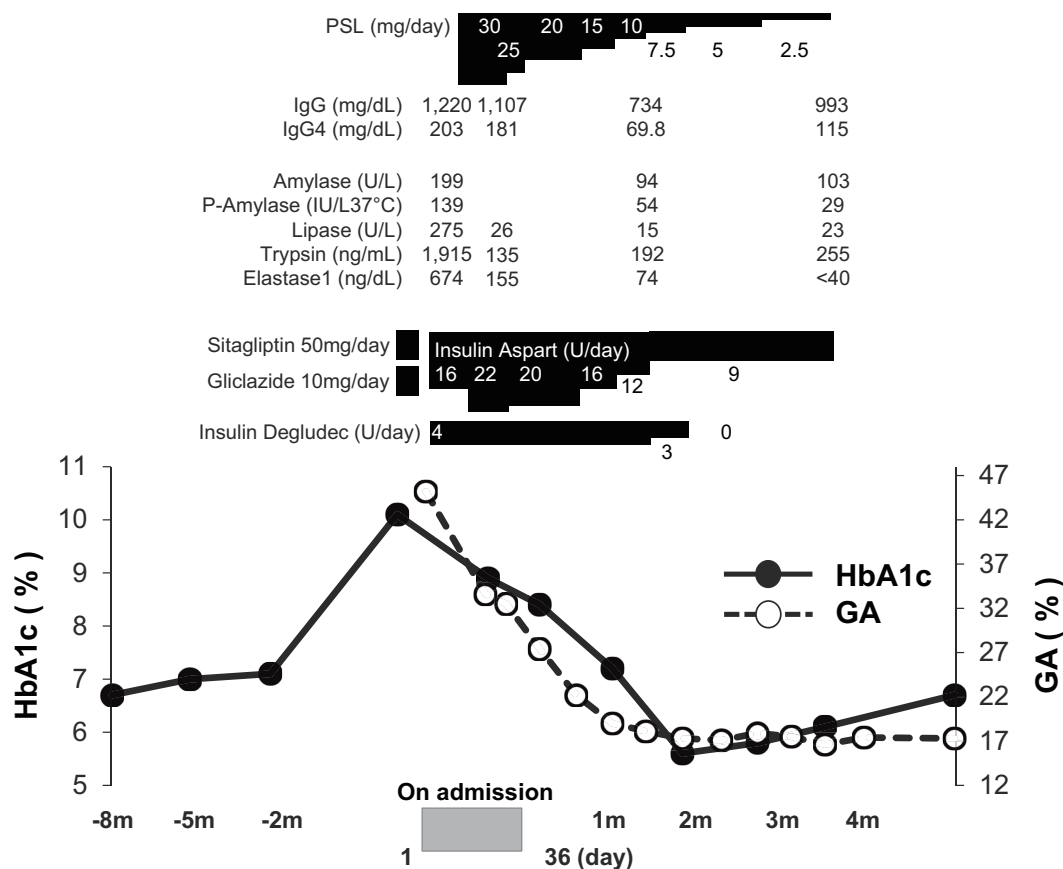
Figure 3. The clinical time course. Increased HbA1c levels were observed on admission. After admission, we started insulin therapy instead of oral anti-diabetic agents. In addition, after the diagnosis of autoimmune pancreatitis was made, we started glucocorticoid therapy. The pancreatitis markers and IgG4 levels subsequently decreased. We tapered the prednisolone dose and finally stopped steroid therapy about four months later. Since the glycemic control had also been markedly ameliorated, we stopped insulin therapy about four months later as well and continued only diet therapy. PSL: prednisolone, HbA1c: hemoglobin A1c, GA: glycoalbumin

Discussion

We reported the aggravation of glycemic control in a subject with T2DM that was likely associated with the onset of autoimmune pancreatitis. Although this subject had T2DM, he had only received diet therapy, and his glycemic control had been good for about 10 years. Therefore, we feel it is very likely that the aggravation of his T2DM was triggered by the onset of autoimmune pancreatitis. This case report reminds us that glycemic control can be significantly aggravated by the onset of autoimmune pancreatitis.

Pancreatic pathology of autoimmune pancreatitis is characterized by remarkable fibrosis and inflammatory cell infiltration surrounding acinar and ductal cells (7). Glucocorticoid therapy is considered effective for treating autoimmune pancreatitis. However, autoimmune pancreatitis itself and glucocorticoid therapy are risk factors for aggravating glycemic control. In particular, when a subject already has diabetes, glycemic control can be worsened after the onset of autoimmune pancreatitis. In general, it is difficult to improve a patient's glycemic control after the end of glucocorticoid

therapy for autoimmune pancreatitis (5). However, the present patient maintained good glycemic control even after the end of glucocorticoid therapy. Our patient developed prostatitis at 71 years of age. While he did not undergo any therapy for it, abdominal CT had been regularly performed. On abdominal CT taken five months before his presentation, there had been no abnormality in the pancreas (Fig. 1). Based on this admittedly circumstantial evidence, it is likely that the autoimmune pancreatitis in this subject had been in a relatively early stage when his glycemic control was aggravated, although at present, there is no classification system for autoimmune pancreatitis and no specific factor determining the disease stage.

Autoimmune pancreatitis induces the deterioration of the pancreatic β-cell function and thereby aggravates glycemic control. In the present subject, however, we promptly started steroid therapy for autoimmune pancreatitis, which ultimately led to the amelioration of glycemic control. Although steroid therapy itself aggravates glycemic control as a side effect, we believe that promptly starting steroid therapy mitigated autoimmune pancreatitis through the immunosuppressive effects and/or anti-inflammatory action of the treatment,

which may have led to the amelioration of glycemic control in the present subject. Such immunosuppressive and anti-inflammatory effects of steroid may thus have outweighed its adverse effects on the glucose metabolism. In addition, the insulin therapy we introduced in this subject may also have contributed, at least in part, to the preservation of the pancreatic β-cell function. Glucocorticoid therapy at an early stage of autoimmune pancreatitis may therefore be very important for preserving the insulin secretory capacity and improving the glycemic control.

Many patients with autoimmune pancreatitis have a history of diabetes treatment. There have been several conflicting reports describing the aggravation or conversely the improvement of glycemic control after glucocorticoid therapy in patients with autoimmune pancreatitis (4-6, 8-11). Indeed, it was reported that, in subjects with autoimmune pancreatitis and DM, the glycemic control was aggravated after starting glucocorticoid therapy, although other reports described the improvement of glycemic control after glucocorticoid therapy. Since the duration of autoimmune pancreatitis and DM in the patients in those studies was not clear, it is possible that the patients had suffered from autoimmune pancreatitis and/or DM for a long period of time. Under such conditions, the pancreas may have been gradually destroyed by autoimmune pancreatitis, which may explain the relatively little improvement in the pancreatic function and glycemic control after glucocorticoid therapy. In addition, since many of those studies were conducted retrospectively, the precise time course and/or mechanism underlying the observed effects was unclear. We therefore believe that the present report documents a rare and important case in which the destruction of the pancreas was prevented and the insulin secretory function preserved by promptly starting steroid therapy, leading to the marked improvement of glycemic control. However, further studies will be required in order to precisely evaluate the effects of glucocorticoid therapy.

Taken together, the present findings suggest that glycemic control can be aggravated by the onset of autoimmune pancreatitis and/or subsequent introduction of steroid therapy. In addition, it is very important to immediately start glucocorticoid therapy in order to preserve the pancreatic function and ameliorate glycemic control, especially in subjects with T2DM.

The authors state that they have no Conflict of Interest (COI).

References

1. Yoshida K, Toki F, Takeuchi T, et al. Chronic pancreatitis caused by an autoimmune abnormality. Proposal of the concept of autoimmune pancreatitis. Dig Dis Sci **40**: 1561-1568, 1995.
2. Okazaki K, Tomiyama T, Mitsuyama T, et al. Diagnosis and classification of autoimmune pancreatitis. Autoimmun Rev **13**: 451-458, 2014.
3. Matsubayashi H, Kakushima N, Takizawa K, et al. Diagnosis of autoimmune pancreatitis. World J Gastroenterol **20**: 16559-16569, 2014.
4. Nishimori I, Tamakoshi A, Kawa S, et al. Influence of steroid therapy on the course of diabetes mellitus in patients with autoimmune pancreatitis: findings from a nationwide survey in Japan. Research Committee on Intractable Pancreatic Diseases, the Ministry of Health and Welfare of Japan. Pancreas **32**: 244-248, 2006.
5. Miyazawa M, Takatori H, Shimakami T, et al. Prognosis of type 1 autoimmune pancreatitis after corticosteroid therapy-induced remission in terms of relapse and diabetes mellitus. PLoS One **12**: e0188549, 2017.
6. Hirano K, Isogawa A, Tada M, et al. Long-term prognosis of autoimmune pancreatitis in terms of glucose tolerance. Pancreas **41**: 691-695, 2012.
7. Farris AB 3rd, Lauwers GY, Deshpande V. Autoimmune pancreatitis-related diabetes: quantitative analysis of endocrine islet cells and inflammatory infiltrate. Virchows Arch **457**: 329-336, 2010.
8. Nishino T, Toki F, Oyama H, et al. Long-term outcome of autoimmune pancreatitis after oral prednisolone therapy. Intern Med **45**: 497-501, 2006.
9. Tanaka S, Kobayashi T, Nakanishi K, et al. Corticosteroid-responsive diabetes mellitus associated with autoimmune pancreatitis. Lancet **356**: 910-911, 2000.
10. Ketikoglou IG, Elefsiniotis IS, Vezali EV, et al. Diabetes mellitus responsive to corticosteroids in autoimmune pancreatitis. J Clin Gastroenterol **38**: 910, 2004.
11. Takeshima K, Ariyasu H, Iwakura H, et al. Predominant improvement of alpha cell function after steroid therapy in a patient with autoimmune pancreatitis: case report. Diabetes Ther **9**: 1385-1395, 2018.