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【 CASE REPORT 】

Co-existing of Neuromyelitis Optica and Fulminant Type 1 Diabetes

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Abstract:
The patient was a 71-year-old woman with aquaporin-4-antibody positive neuromyelitis optica (NMO), with no history of diabetes. On admission, although she showed an extremely elevated plasma glucose level (1,080 mg/dL), her hemoglobin A1c level was low (7.1%), which indicated the rapid progression of diabetes. She also showed ketoacidosis and had a human leukocyte antigen haplotype, DRB1*09:01-DQB1*03:03 associated with Fulminant type 1 diabetes (FT1D). Based on these results, the patient was diagnosed with FT1D. We herein describe the first reported case of a patient with FT1D with NMO, which raises the possibility that T-cell-mediated autoimmunity is involved in the pathogenesis of both FT1D and NMO.

Key words: type 1 diabetes mellitus, neuromyelitis optica, diabetic ketoacidosis

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Introduction

Fulminant type 1 diabetes (FT1D) is a subtype of ketosis-onset type 1 diabetes that is characterized by the extremely rapid progression of hyperglycemia and ketosis/ketoacidosis caused by the destruction of almost all pancreatic β cells. It has been established as a subtype of idiopathic type 1 diabetes mellitus (T1DM) (1, 2). Several reports indicate that genetic factors, such as human leukocyte antigen (HLA), and environmental factors, such as viral infections, contribute to the development of this disease (3, 4). Glycemic control is usually difficult to achieve in FT1D patients because their endogenous insulin is completely depleted; thus, we must pay special attention to the development of FT1D in the clinical setting (5).

Neuromyelitis optica (NMO) and neuromyelitis optica spectrum disorders (NMOSDs) are inflammatory disorders of the central nervous system (CNS) characterized by severe, immune-mediated demyelination and axonal damage predominantly targeting the optic nerves and spinal cord (6). The discovery of a disease-specific serum NMO-immunoglobulin G (IgG) antibody that selectively binds aquaporin-4 (AQP4) has increased the understanding of a diverse spectrum of disorders (7). NMO is still an incurable disease. The goals of treating acute NMO events are to improve relapse symptoms and restore neurological functions; long-term immunosuppression aims to prevent further attacks (6). FT1D is known to often accompany autoimmune diseases other than NMO (5). We herein report a case of FT 1D that was observed during follow-up for NMO.

Case Report

A 71-year-old woman with NMO was referred to our department because of a 1-week history of vomiting and diarrhea. She also presented with overnight thirst. Although she continued to receive prednisolone (15 mg/day) for 1 year after the diagnosis of NMO, she had no history or evidence of diabetes mellitus. That is, her blood glucose levels had remained within a normal range until the last blood examination, which was carried out 3 months before her referral.

On physical examination, the patient's blood pressure was 91/56 mmHg, her pulse was 100 beats/min, and her body

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Table. The Laboratory Results of the Patient.

Variable			Reference range	Variable			Refenrence range
Comlete blood count (On admission)				Arterial blood gas analysis (Room air, On admission)			
White blood cell count	(/μL)	23,810	47.0-87.0	pH		7.08	7.35-7.45
Red blood cells	($\times10^4$/μL)	413	370-490	pCO2	mmHg	13.5	32-45
Hemoglobin	(g/dL)	12.7	11.0-15.0	pO2	mmHg	121.1	83-108
Hematocrit	(%)	39.7	35.0-45.0	Bicarbonate	mmol/L	3.9	21.2-27.0
Platelet count	($\times10^4$/μL)	39	15.0-35.0	Base excess	mmol/L	-24	-2.3-2.7
Biochemistry(On admission)				Diabetes-related examination			
Total protein	(g/dL)	6.4	6.5-8.2	Glucose	(mg/dL)	1,054	70-109
Albumin	(g/dL)	3.8	3.5-5.5	HbA1c(3 months			
Blood urea nitrogen	(mg/dL)	57.8	7.0-20.0	before admission)	(%)	6.4	4.6-6.2
Creatinine	(mg/dL)	2.1	0.5-1.0	HbA1c(On admission)	(%)	7.1	4.6-6.2
Amylase	(U/L)	1,319	30-140	3-OHBA	(μmol/L)	10,114	59-115
Lipase	(U/L)	73	13-55	Acetoacetic acid	(μmol/L)	3,972	41-89
Elastase-1	(ng/dL)	3,773	0-300	ΔCPR(6 min) during			
GOT	(U/L)	12	10-35	Glucagon stimulation			
GPT	(U/L)	23	5-40	test(10th day)	(ng/mL)	0.2	>0.5
GGTP	(U/L)	72	0-30	Urinary ketone		+++	
Na	(mmol/L)	132	135-146	Serum CPR(1th day)	(ng/mL)	0.37	0.43-2.35
K	(mmol/L)	6.5	3.5-4.6	Serum CPR(10th day)	(ng/mL)	0.2	0.43-2.35
Cl	(mmol/L)	97	96-110	Urinary CPR(9th day)	(μg/day)	3.7	17-181
DNA typing				Anti-GAD antibody		negative	
DRB1*09:01-DQB1*03:03				Anti-IA-2 antibody		negative	
DRB1*13:02-DQB1*06:04				Serological testing for virus			
neuromyelitis optica-related examination (On Diagnosis)				Coxsackie B3		<4.0	<4.0
ant-aquaporin-4 antibody	(U/mL)	18.2	<3	Coxsackie B4		<4.0	<4.0

CPR: C-peptide Immunoreactivity, GAD: Glutamic Acid Decarboxylase, IA-2: Insulinoma-associated Antigen-2, GOT: Glutamate Oxaloacetate Transaminase, GPT: Glutamic Pyruvic Transaminase, 3-OHBA: 3-hydroxybutyric acid

temperature was 36.1℃. Her weight and height were 44.6 kg and 154 cm, respectively. She showed drowsiness, Kussmaul breathing, and no abdominal tenderness. Her mouth was dry, and her skin turgor was poor. The remaining findings of the neurological and general examinations were unremarkable. Her laboratory test data are shown in Table. The patient had hyperglycemia (1,080 mg/dL), a remarkable increase in ketone bodies in the urine and blood, and metabolic acidosis with a high anion gap. Based on these results, the patient was diagnosed with diabetic ketoacidosis (DKA). Although her plasma blood glucose level was high, her hemoglobin A1c (HbA1c) level was low (7.1%), suggesting the rapid progression of hyperglycemia. Abdominal computed tomography showed no pancreatic abnormalities. Her urinary C-peptide excretion (3.7 μg/day) and a glucagon stimulation test both revealed severely impaired insulin secretion. Tests for various islet-related autoantibodies were negative. Serological testing for several viruses was performed, and tests for Coxsackie B3 and B4 were negative. HLA typing showed that she was heterozygous for DRB1*09:01-DQB1*03:03. Based on these findings, we diagnosed the patient with FT1D.

The patient was treated with an intravenous fluid infusion and a continuous infusion of insulin. After these treatments, her physical condition and consciousness showed a rapid improvement. On the sixth hospital day, she was switched to multiple daily injections of insulin (Figure). Her diabetes has remained well controlled since then.

Discussion

We described the case of an elderly female patient with FT1D complicated by NMO. FT1D is characterized by rapid-onset diabetic ketoacidosis, low HbA1c, undetectable serum C-peptide, and negativity for islet-related autoantibodies (1); it is proposed as a novel subtype of idiopathic (type 1B) diabetes mellitus (8). Our clinical findings in this case were consistent with the diagnostic criteria for FT1D (9). In Japan, FT1D accounts for 0.2% of all new-onset diabetes cases, and 14.8-19.6% of acute-onset type 1 diabetes cases (10, 11). The most common symptoms are similar to those of the common cold, such as thirst (93.7%); abdominal symptoms such as nausea, vomiting, and abdominal pain (72.5%); flu-like symptoms (71.7%); and drowsiness (45.2%) (2). The pathogenesis of FT1D is influenced by genetic and environmental factors. Regarding genetic factors, HLA class II genes are strongly associated with susceptibility to progression to FT1D. The HLA DR4-DQ4 haplotype is common in Japanese individuals, but is rare in the Caucasian populations and might contribute to the different inci-

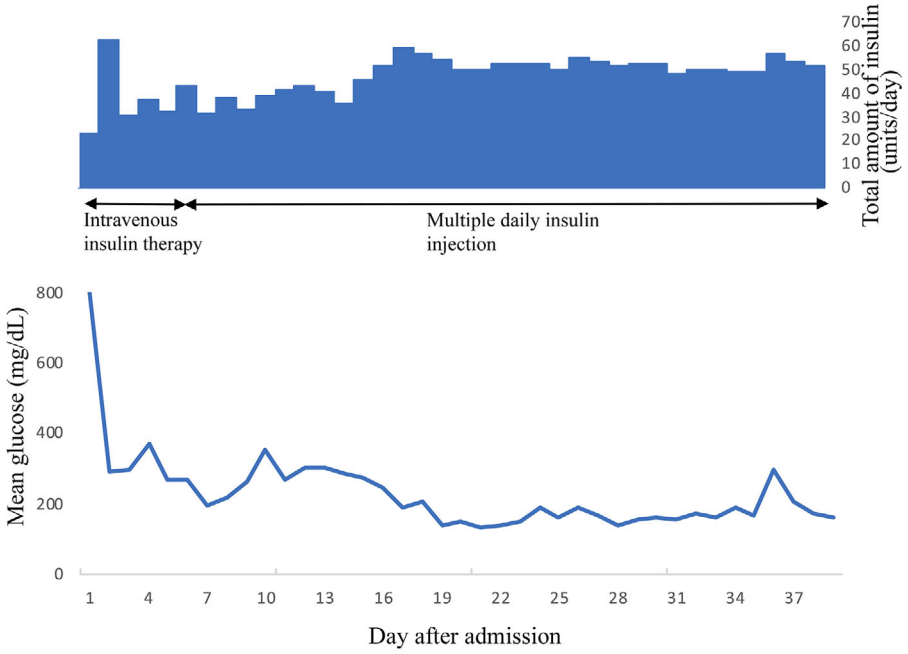

Figure. **The clinical course of insulin therapy. The upper panel shows the total insulin dose. The lower panel shows the mean glucose levels during the clinical course.**

dences of FT1D between Japanese and Caucasian populations. Imagawa et al. reported that the frequency of HLA-DR4, but not -DR9, was significantly higher in FT1D, while the frequencies of HLA-DR1, -DR2, -DR5, and -DR8 were significantly lower. In contrast, DR9 but not DR4 was more frequent, and DR2 was extremely rare in T1DM (3). Additionally, a recent report indicated that the frequencies of the DRB1*04:05-DQB1*04:01 and DRB1*09:01-DQB1*03:03 haplotypes were significantly higher, and those of the DRB1 *01:01-DQB1:05:01, DRB1:15:02-DQB1*06:01 and DRB1* 08:03-DQB1*06:01 haplotypes were significantly lower in patients with FT1D than in the control subjects (4). Our patient also exhibited this typical HLA type. With regard to environmental factors, viral infections can trigger an accelerated immune reaction against infected β-cells, causing massive β-cell death and FT1D (12). In particular, enteroviral infection is related to the development of FT1D (3). In this case, we did not test for every viral infection, such as parainfluenza virus, enterovirus, Coxsackie virus, or human herpes virus 6 or 7. However, physicians should consider FT 1D when viral infections are prevalent.

NMO is an autoimmune water channelopathy that predominantly affects astrocytes in the CNS, resulting in secondary demyelination, preferentially attacking the optic nerve, spinal cord, and circumventricular organs (6). It is recognized as an inflammatory demyelinating disease (IDD). After AQP4-IgG was discovered as the first serum biomarker of any IDD in 2004, it became accepted that the NMO entity is distinct from multiple sclerosis (13). Immunologic, epidemiologic, and pathologic evidence suggests that T cells play an important role in the etiology of NMO (14). Pathogenic AQP4-specific antibodies in NMO serum are predominantly IgG1, a T cell-dependent IgG subclass, and T cell-mediated CNS inflammation permits the entry of these antibodies into the CNS. In certain populations, NMO susceptibility is associated with allelic major histocompatibility complex II genes: in particular, HLA-DR17 (DRB1*0301). AQP4-specific T cells have been identified in patients, and T cells specific for dominant AQP4 epitopes exhibit Th17 polarization (7, 14).

Various autoimmune diseases have been reported in up to 30% of patients with NMO, suggesting that individuals with this condition might have a genetic predisposition to aberrant autoimmunity (14). However, a previous study demonstrated that none of 98 patients with NMO had diabetes, stiff-man syndrome, or epilepsy. All 98 patients tested positive for AQP4 antibodies. No patients tested positive for glutamic acid decarboxylase 65 or N-methyl-D-aspartate receptor antibodies (15). Although there is no direct common etiology indicated between FT1D and NMO, several lines of evidence have shown that these diseases might have a causal relationship. A previous report presented the case of a patient who developed type 1 diabetes mellitus and severe optic neuritis with AQP4 antibodies during treatment with combinations of drugs, including interferon (IFN)-α and IFN-γ for chronic hepatitis C (16). A more recent report described the first patient who developed anti-AQP4 antibody-positive NMO spectrum disorders as an anti-programmed cell death-1 (PD-1) antibody and nivolumab-induced immune-related adverse events (irAE) (17). PD-1 and programmed cell death-ligand-1 (PD-L1) inhibitors have been highlighted in the field of cancer treatment. The interaction between PD-1 and PD-L1 is thought to play an important role in the regulation of the self-immune tolerance mechanism, so blocking these molecules may cause serious irAEs, including FT1D (18). Hughes et al. described the develop-

ment of new-onset insulin-dependent diabetes in five patients after receiving anti-PD-1 antibodies, either as single agents or in combination with other cancer drugs (19). Several lines of evidence have indicated that regulatory T cells play a central role in suppressing the T cell-mediated immune response and the development of FT1D. Massive cellular infiltration of T cells and macrophages has been detected in islets and exocrine pancreas immediately after FT1 D onset. Recently, it was reported that $CD^{4+}CD45RA^{-}Foxp3^{hi}$-activated regulatory T cells - which play a central role in the T cell - mediated immune response-are functionally impaired in patients with FT1D (20). These findings suggested that both innate and acquired immune disorders might contribute to the development of FT1D. In this report, we pointed out the first patient with FT1D and NMO, raising the possibility that T cell-mediated autoimmunity is involved in the pathogenesis of both FT1D and NMO.

Conclusion

We reported the first case of FT1D complicated with NMO. FT1D is a life-threatening complication if treatment is delayed or the patient cannot be treated. Hence, careful consideration of the differential diagnosis is critical in patients with NMO who present with hyperglycemia. It is difficult to draw strong conclusions regarding the relationship between FT1D and NMO. This case report might raise the possibility that T cell-mediated autoimmunity is involved in the pathogenesis of both FT1D and NMO.

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

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