JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
LETTER TO THE EDITOR

Onset of fulminant type 1 diabetes mellitus under immunotolerance status after long-term therapy for chronic inflammatory demyelinating polyneuropathy

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a progressive and relapsing disease causing weakness and sensory loss[1]. Such symptoms are likely due to autoimmune inflammation in peripheral nerves, but specific antigens and autoantibodies have not yet been identified.

A 56-year-old man with an 8-year history of CIDP had thirst and general fatigue. He repeated the recurrence and remission of CIPD, and had intravenous immunoglobulin therapy repeatedly (30 g/day × 5 days for remission induction, 30 g/day every other week × 7 days for maintenance, 30 g/day × 10 days for first recurrence, 30 g/day × 6 days for second recurrence and 30 g/day × 5 days for third recurrence). Furthermore, he had plasma apheresis therapy once, steroid pulse therapy twice (1,000 mg/day of methylprednisolone), immunosuppressant therapy (3 mg/day of tacrolimus, 150 mg/day of azathioprine, 4 mg/day of methotrexate and 300 mg/day of ciclosporin pulse therapy) and oral prednisolone therapy during 8 years. His symptoms (numbness of arms and legs) were stable for the past 8 months with the treatment of 30 mg/day of prednisolone every other day.

His height and bodyweight were 166.0 cm and 70.0 kg. Heart rate and blood pressure were 117 b.p.m. and 111/60 mmHg. Table 1 shows the laboratory data. Although the patient's hemoglobin A1c level was 5.9% 1 month earlier, his plasma glucose level was 816 mg/dL and hemoglobin A1c level was 6.4% at admission. He had ketoacidosis, and all autoantibodies were negative. Although abdominal computed tomography did not show remarkable findings, pancreatic enzyme levels were elevated. We diagnosed him with fulminant type 1 diabetes mellitus (FT1DM)[2]. In addition, we measured his cytokine levels 1 week after the onset of fulminant type 1 diabetes mellitus. As shown in Table 1, both inflammatory and anti-inflammatory cytokine levels were very low (interleukin [IL]-1β, <10 pg/mL [normal range <10 pg/mL]; IL-4, 10.0 pg/mL [<6.0 pg/mL]; IL-6, 1.6 pg/mL [<4 pg/mL]; IL-8, 3.0 pg/mL [<2.0 pg/mL]; IL-10, 3.0 pg/mL [<5 pg/mL]; IL-12, <7.8 pg/mL [<7.8 pg/mL]; IL-18, 371 pg/mL [126 ± 44.5 pg/mL]; interferon-γ, <0.1 U/mL [<0.1 U/mL]; tumor necrosis factor-α, 0.6 pg/mL [0.6–2.8 pg/mL]). Although it is not certain that the data within the normal range truly indicate immunotolerance status, it seems that such data are, at least partially, associated with immunotolerance status after long-term therapy for CIDP. It is also possible that such cytokine levels were influenced by fulminant type 1 diabetes mellitus or CIPD itself. After starting insulin therapy, hyperglycemia and ketoacidosis were improved. As the Coxsackie virus group A type 5 antibody value was relatively higher at the onset of fulminant type 1 diabetes mellitus (titer: 16) compared with 4 months later (titer: 4), its onset was possibly associated with Coxsackie virus infection.

It is known that fulminant type 1 diabetes mellitus is complicated in patients with drug-induced hypersensitivity syndrome and its therapy with steroids, but its precise mechanism remains unknown[3]. We assume that the onset of fulminant type 1 diabetes mellitus is associated with immunotolerance status induced by the treatment for drug-induced hypersensitivity syndrome. Furthermore, recently much attention has been paid to fulminant type 1 diabetes mellitus being induced during treatment with programmed cell death 1 antibody. It is thought that the immunotolerance status after programmed cell death 1 antibody therapy is closely associated with the onset of fulminant type 1 diabetes mellitus[4]. Therefore, we assume that the present patient was also under immunotolerance status after long-term therapy for CIDP, which led to the onset of fulminant type 1 diabetes mellitus. Indeed, both inflammatory and anti-inflammatory cytokine levels were very low. In addition, this patient had Coxsackie virus infection and fulminant type 1 diabetes mellitus-associated human leukocyte antigen type[5]. Therefore, we believe not only immunotolerance status, but also virus infection and human leukocyte antigen type were involved in the onset of fulminant type 1 diabetes mellitus in this patient.

This is the first case report of newly onset fulminant type 1 diabetes mellitus in

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Received 11 November 2017; revised 11 December 2017; accepted 22 December 2017

Table 1 | Laboratory data on admission in the patient

Variable	Result	Reference range	Variable	Result	Reference range
Peripheral blood			Diabetes marker		
White blood cells (/μL)	13,000	4,000–9,000	Plasma glucose (mg/dL)	816	70–110
Neutrophil (%)	92.0	28.0–78.0	Hemoglobin A1c (%)	6.4	4.6–6.2
Red blood cells ($\times 10^4$/μL)	494	427–570	Insulin (μU/mL)	1.04	1.84–12.2
Hemoglobin (g/dL)	15.0	14.0–18.0	C-peptide (ng/mL)	0.29	0.61–2.09
Platelets ($\times 10^4$/μL)	35.6	15.0–35.0	GAD antibody (U/mL)	<5.0	0–4.9
Blood biochemistry			IA-2 antibody (U/mL)	<0.4	0–0.3
Total protein (g/dL)	7.7	6.7–8.3	ICA (U)	<1.25	<1.25
Albumin (g/dL)	5.0	3.8–5.2	Insulin antibody (U/mL)	<0.4	0–0.3
Total bilirubin (mg/dL)	1.42	0.00–1.00	Anti-nuclear antibody	<40	0–39
AST (U/L)	18	8–35	HLA-DNA typing	HLA-DRB1*04:05-DQB1*04:01	
ALT (U/L)	38	5–43	Endocrine marker		
LDH (U/L)	154	106–211	ACTH (pg/mL)	10.5	7.2–63.3
ALP (U/L)	216	104–338	Cortisol (μg/dL)	3.61	6.24–18.0
γ-GTP (U/L)	117	2–72	DHEA-S (μg/dL)	62	76–386
Cholinesterase (U/L)	420	170–430	TSH (μU/mL)	0.3319	0.35–4.94
Creatinine (mg/dL)	1.42	0.3–1.1	Free thyroxine (ng/dL)	1.27	0.70–1.48
BUN (mg/dL)	44.8	8.0–20.0	Aldosterone (pg/mL)	81.9	35.7–240
CRP (mg/dL)	1.89	0.00–0.50	Renin activity (ng/mL/h)	0.7	0.3–2.9
Sodium (mEq/L)	126	135–148	Urinary test		
Potassium (mEq/L)	6.1	3.3–5.0	Urinary pH	5.0	
Chloride (mEq/L)	88	98–109	Urinary protein	±	
Calcium (mg/dL)	9.8	8.2–11.0	Urinary sugar	4+	
Phosphorus (mg/dL)	8.3	2.5–4.5	Urinary ketone body	2+	
Amylase (U/L)	130	40–134	Inflammatory and anti-inflammatory cytokine		
P-amylase (U/L)	41	20–65	IL-1β (pg/mL)	<10	<10
Elastase-1 (ng/dL)	968	0–300	IL-4 (pg/mL)	10.0	<6.0
P-phospholipase A2 (ng/dL)	789	130–400	IL-6 (pg/mL)	1.6	<4.0
Blood gas aspiration			IL-8 (pg/mL)	3.0	<2.0
pH	7.208	7.35–7.45	IL-10 (pg/mL)	3.0	<5.0
PCO_2 (mmHg)	20.7	35.0–45.0	IL-12 (pg/mL)	<7.8	<7.8
PO_2 (mmHg)	91.2	80.0–100.0	IL-18 (pg/mL)	371	81–171
HCO_3^- (mEq/L)	7.9	22.0–28.0	IFN-γ (U/mL)	<0.1	<0.1
Base excess (mmol/L)	−17.8	−2.3–2.3	TNF-α (pg/mL)	0.6	0.6–2.8

γ-GTP, γ-glutamyltranspeptidase; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CRP, C-reactive protein; DHEA-S, dehydroepiandrosterone sulfate; GAD antibody, anti-glutamic acid decarboxylase; HLA-DNA, human leukocyte antigen deoxyribonucleic acid; IA-2, anti-insulinoma-associated tyrosine phosphatase-like protein-2; ICA, anti-islet cell antigen; IFN, interferon; IL, interleukin; LDH, lactate dehydrogenase; P-amylase, pancreatic amylase; P-phospholipase A2, pancreatic phospholipase A2; TNF, tumor necrosis factor; TSH, thyroid stimulating hormone.

a patient with CIDP treated with steroids. We should be aware of the possibility of fulminant type 1 diabetes mellitus under immunotolerance status when we examine patients with immunotolerance status.

ACKNOWLEDGMENT

There was no funding for this work.

DISCLOSURE

The authors declare no conflict of interest.

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Doi: 10.1111/jdi.12796