

NOTE

A case report of fulminant type 1 diabetes mellitus associated with drug-induced hypersensitivity syndrome in an elderly patient with coxsackie B4 virus infection and human leukocyte antigen-A24 haplotype

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Abstract. Drug-induced hypersensitivity syndrome (DIHS) is a severe systemic adverse drug reaction. Previous studies showed that DIHS is associated with the onset of fulminant type 1 diabetes mellitus (FT1D). Although genetic background and abnormalities in immune response or viral infection are considered to be associated with pathogenesis of FT1D, it remains unclear whether virus infection and specific human leukocyte antigen (HLA) typing are involved in DIHS-associated FT1D. Here, we report a case of a 78-year-old female patient with FT1D after DIHS treatment. She was diagnosed as DIHS caused by carbamazepine, and treatment with prednisolone was initiated. After 46 days from the occurrence of DIHS, she was admitted to our hospital because of type 1 diabetes mellitus and diabetic ketoacidosis. Although her Hemoglobin A1c (HbA1c) was elevated by prednisolone treatment (HbA1c: 9.2%), we diagnosed her as fulminant type 1 diabetes mellitus considering the abrupt onset of the ketoacidosis. Her general condition was improved by treatment with fluid infusion and insulin administration. During her clinical course, the infection of coxsackie B4 virus was observed. In addition, the examination of HLA typing showed HLA-A24 haplotype. These findings suggest that the coxsackie B4 virus infection may be involved in the pathogenesis of DIHS-induced FT1D, and that HLA-A24 haplotype might relate to DIHS-associated FT1D.

Key words: Fulminant type 1 diabetes mellitus, Drug-induced hypersensitivity syndrome, Coxsackie virus B4

FULMINANT TYPE 1 DIABETES MELLITUS (FT1D) is a subtype of type 1 diabetes mellitus characterized by extremely rapid progression of hyperglycemia and diabetic ketoacidosis (DKA) due to almost complete pancreatic beta-cell destruction [1, 2]. Because FT1D often causes poor prognosis, we have to pay special attention to the development of FT1D in clinical settings. Drug-induced hypersensitivity syndrome (DIHS) is a severe systemic adverse drug reaction characterized by rash, fever, leukocytosis, eosinophilia and liver injury [3, 4]. Reactivation of human herpes virus 6 (HHV-6) is one

of specific characteristics of DIHS [3]. Recently, it is reported that FT1D sometimes occurs after DIHS treatment [4, 5]. Indeed, Onuma *et al.* previously reported that the clinical characteristics of FT1D with DIHS were similar to those without DIHS, but the frequency was much higher than that in the general population (0.54% vs. 0.01%) [4]. Because the mechanism of DIHS-associated FT1D still remains unclear, the investigation of clinical characteristics including genetic background and serological testing for viral infection are necessary to clarify this issue.

Case Report

A 78-year-old female patient visited a clinic for her blepharospasm and was prescribed carbamazepine. One month later, maculopapular rash occurred in her face,

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trunk, and extremities. She was admitted to the department of dermatology in our hospital. Although she did not have high grade fever (37.4°C), lymphadenopathy, eosinophilia or lymphocytosis, she met a possible case of DIHS by European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) [6] based on maculopapular rash after medication of carbamazepine, liver dysfunction (aspartate aminotransferase 39 U/L; normal range 13–30 U/L, alanine aminotransferase 31 U/L; normal range 7–23 U/L) and exclusion of other alternative diseases. Because DIHS caused by carbamazepine was suspected, carbamazepine was discontinued and administration of prednisolone (PSL) 40 mg/day was initiated. Her hemoglobin A1c (HbA1c) level was 6.2% on the admission. Thereafter, her rash was improved; thus the dose of PSL was gradually tapered. In the clinical course, the titer of anti-HHV-6 IgG was increased to 40:640 (16-fold increase) and the drug-induced lymphocyte stimulation test (DLST) for carbamazepine was positive; thus carbamazepine-induced DIHS was confirmed. Her plasma glucose levels at evening and night were increased up to 200 to 250 mg/dL after the PSL administration. Because PSL dose was decreased to 10 mg/day, she was discharged without any anti-diabetic drugs.

After 46 days from the occurrence of DIHS, she was taken to our hospital because of unconsciousness. On physical examination, Glasgow coma scale was E3V4M6. Her body temperature was 35.6°C and other vital signs were fortunately within normal range. Her skin turgor was decreased. She did not have abdominal pain. Laboratory examination showed hyperglycemia (plasma glucose: 649 mg/dL and HbA1c 9.2%) and metabolic acidosis (pH: 7.338, HCO₃: 13.7 mmol/L), and urine ketone was 4 plus; therefore, we diagnosed DKA. We promptly started fluid infusion and insulin administration. Although all of anti-islet antibodies (anti-glutamic acid decarboxylase antibody, anti-insulinoma-associated antigen-2 antibody, insulin autoantibody, anti-zinc transporter 8 antibody, and islet cell cytoplasmic autoantibody) were negative, her insulin secretory function was extremely inhibited; urine C-peptide 1.8 µg/day at fifth hospital day and 1.2 µg/day at 28th hospital day (normal range; 24–97 µg/day), and no response for glucagon loading test (serum C-peptide <0.2 ng/mL at basal and 0.2 ng/mL at 6 min). Serum amylase was increased (178 U/L; normal range 44 to 132 U/L). Although her HbA1c was elevated by PSL treatment for DIHS, we diagnosed as FT1D according to its criteria [7].

Serological Testing for Virus Infections

To investigate the association between viral infection and FT1D, we performed serological testing for several viruses such as, herpes viruses, parainfluenza virus B1-3, coxsackie virus A2-7, 9, 10, 16 and B1-6, at 11 and 54 days after the admission (Table 1). Coxsackie B4 virus antibody titer was significantly elevated from 1:<4 to 1:64 (16-fold increase), whereas all other antibodies were not altered.

HLA Typing

Furthermore, we examined her human leukocyte antigen (HLA) typing. The HLA haplotyping was performed with HLA typing kits of Scisco Genetics Inc (Seattle, WA). Exon 1 to 7 of HLA-A, B and C, as well as exon 1 to 4 of HLA-DR, DQ and DP were examined by next generation sequencing with MiSeq (Illumina, San Diego, CA). The results were analyzed by using a software GeMS HLA (Scisco Genetics Inc., Seattle, WA). HLA-A*11:01/24:02, B*40:02/67:01, DRB1*15:01/-, DQA1*01:02/-, and DQB1*06:02/- were identified.

Discussion

We described a case of elder female patient who had FT1D associated with carbamazepine-induced DIHS. The serological testing showed that the antibody titer of coxsackie B4 virus, but not others, was significantly elevated in the clinical course, suggesting that infection of coxsackie B4 virus may be involved in the pathogenesis of FT1D. Although the pathogenesis of FT1D remains to be elucidated, it is suggested that viral infection plays important roles in its onset [8]. Akatsuka *et al.* previously reported a case of 39-year-old women with FT1D and coxsackie B4 virus infection [9]. The patient had 8-fold increase in the plasma titer of coxsackie B4 virus neutralizing antibody after 4 weeks from FT1D diagnosis. However, to our knowledge, there are no other reports to indicate the association between FT1D and coxsackie B4 virus infection. In our case of DIHS-induced FT1D, the antibody titer of coxsackie B4 virus was increased up to 16-fold increase. These cases suggest that abnormal immune responses to coxsackie B4 virus infection may lead to the pathogenesis of FT1D. However, it is unclear whether DIHS or susceptibility by PSL treatment induced the infection of coxsackie B4 virus in our case. Moreover, we diagnosed as DIHS

Table 1 Virus antibody titers

	First test	Second test		First test	Second test
CMV-IgG	38.2	107	Coxsackie A2	64	16
CMV-IgM	0.79	0.68	Coxsackie A3	8	16
EB VCA-IgG	20	20	Coxsackie A4	<4	8
EB VCA IgM	10	<10	Coxsackie A5	16	16
EBNA	10	10	Coxsackie A6	<4	4
HHV-6 IgG	320	160	Coxsackie A7	8	16
HHV-6 IgM	<4	<10	Coxsackie A9	<4	<4
HHV-7 IgG	40	40	Coxsackie A10	4	4
HHV-7 IgM	<4	<10	Coxsackie A16	16	16
			Coxsackie B1	<4	<4
Parainfluenza B1	10	<10	Coxsackie B2	<4	8
Parainfluenza B2	40	20	Coxsackie B3	<4	<4
Parainfluenza B3	80	80	Coxsackie B4	<4	64
			Coxsackie B5	<4	<4
			Coxsackie B6	<4	<4

Anti-CMV IgG and anti-CMV IgM were measured by enzyme immunoassay (EIA). Other virus antibodies were measured by fluorescence antibody technique or neutralization test. The serum samples were collected at 11 days and 54 days after the second admission.

according to the European criteria [6] although her symptoms and laboratory findings did not completely meet the Japanese criteria of DIHS [10]. In this case, anti-HHV-6 antibody titer was significantly elevated, which is an important characteristic of DIHS. Further, the immediate initiation of PSL treatment might protect becoming severe stage. Therefore, further studies and accumulation of case reports are necessary to clarify whether DIHS is involved in the incidence of FT1D with coxsackie B4 virus infection.

On the other hand, the genetic background is also important, because not all cases with coxsackie B4 virus infection or DIHS suffer FT1D. Accumulating evidence has shown the association of HLA haplotypes with susceptibility or resistance to development of FT1D [8, 11]. Onuma *et al.* previously showed a higher frequency of HLA-B62 in FT1D with DIHS than that of cases without DIHS [4]. Furthermore, in their study, the frequency of

HLA-A24 tended to be high, although the association was not significant [4]. Our patient had HLA-A24, but not HLA-B62, suggesting that HLA-A24 may confer susceptibility to development of FT1D with DIHS in this case. Of interest, the present case showed HLA-DRB1*15:01 and DQB1*06:02, which have been reported to be resistant haplotypes [11]. It is unknown how these HLA haplotypes contribute to the pathogenesis of DIHS-induced FT1D in this case; thus, further studies are necessary.

This is the first case report suggesting that coxsackie B4 virus infection may be involved in the pathogenesis of DIHS-induced FT1D in elderly patients with HLA-A24 haplotype.

Disclosure

The authors declare no conflict of interest.

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