CASE REPORT

Fulminant type 1 diabetes mellitus associated with a reactivation of Epstein–Barr virus that developed in the course of chemotherapy of multiple myeloma

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ABSTRACT

A 70-year-old woman who was diagnosed with multiple myeloma underwent chemotherapy. Three months after beginning chemotherapy, she was readmitted to the hospital because of fever and hepatopathy. Her elevated Epstein–Barr virus (EBV) antibody levels showed that the hepatopathy was caused by reactivation of EBV. On the 18th hospital day, the levels of fasting plasma glucose (FPG; 451 mg/dL) and pancreatic enzymes were suddenly elevated. Elevation of HbA_{1c} level (6.4%) was slight, as compared with that of the FPG level. Arterial blood gas analysis showed metabolic acidosis and diabetic ketoacidosis was suspected. The serum C-peptide level was below the detectable limit both before and after glucagon load, thereby suggesting an insulin-dependent state. These features were identical to the features for fulminant type 1 diabetes mellitus. The levels of EBV anti-viral capsid antigen immunoglobulin M decreased, and the clinical course was identical to that associated with reactivation of EBV infection. (J Diabetes Invest, doi: 10.1111/j.2040.1124.2010.00061.x, 2010)

INTRODUCTION

Type 1 diabetes mellitus is caused by insulin deficiency arising from the destruction of pancreatic β-cells. Type 1 diabetes mellitus is divided into autoimmune type and idiopathic type. Some patients with idiopathic type 1 diabetes rapidly develop ketoacidosis. This type of disease is know as 'fulminant type 1 diabetes mellitus' [1,2], and it accounts for approximately 20% of the ketosis- or ketoacidosis-onset type 1 diabetes cases[3].

The relationship between the onset of type 1 diabetes and viral infection have been drawing close attention for several years. Viral antibody titers have also been measured in many cases. In this regard, the roles of viruses, such as influenza B[3], Coxsackie-A2, Coxsackie-B4[4], herpes simplex virus-1 (HSV-1), human herpes virus-6 (HHV-6), mumps virus[5] and so on have been studied[6].

We recently encountered a case of fulminant type 1 diabetes in which the onset of disease seemed to have been triggered by reactivation of Epstein–Barr virus (EBV). To date, no case of fulminant type 1 diabetes caused by EBV infection has been reported. Therefore, we have presented this valuable case along with a review of the literature.

CASE REPORT

The patient was a 70-year-old Japanese woman who was diagnosed with multiple myeloma in 2006. She also underwent three courses of vincristine, doxorubicin and dexamethasone therapy, and one course of melphalan and prednisolone therapy. The patient's condition stabilized and she was discharged. However, 7 days after discharge, she visited the hospital again with a high fever (38.6°C). Table 1 shows peripheral blood analysis and biochemical tests. Although no sign of biliary tract dilatation was noted, abdominal ultrasonography showed hepatomegaly and gallbladder atrophy. The titers of EBV antibody and anti-cytomegalovirus (CMV) immunoglobulin G (IgG) were elevated. Elevation of EBV titers indicated reactivation of EBV infection, and antibodies to hepatitis virus and autoimmune hepatitis were negative (Table 1). On the basis of these results, we diagnosed that the patient's condition was caused by EBV reactivation.

The woman was diagnosed with acute hepatopathy and began to undergo rehydration and intravenous treatment with antibiotics (CPZ/SBT). As shown in Figure 1, the patient developed systemic multiform erythema on the fifth hospital day and the lesion gradually showed livedo characteristics (Figure 2). A peripheral blood test on the 18th hospital day showed an increased

Table 1 | Laboratory data on admission

Hematological analysis		Blood chemistry		Urinalysis	
WBC	3680/μL	AST	129 IU/L	pH	5.5
RBC	$280 \times 10^4/\mu L$	ALT	152 IU/L	Glucose	(−)
Hb	10 g/dL	γ-GTP	258 IU/L	Protein	(±)
Hct	30.5%	T-Bil	2 mg/dL	Ketone body	(±)
Plt	$11.3 \times 10^4/\mu L$	ALP	641 IU/L	Occult blood	(2+)
Meta	1%	LDH	418 IU/L	Others	
Stab	24%	P-AMY	25 IU/L	HBs Ag	(−)
Seg	32%	BUN	8.7 mg/dL	HCV Ab	(−)
Lym	19%	Cre	0.6 mg/dL	IgM-HA Ab	0
Mono	20%	TP	5.8 g/dL	EBV anti-VCA IgM (ELISA)	7.6
Eos	1%	Alb	3.8 g/dL	EBV anti-VCA IgG (ELISA)	2.4
Baso	1%	CRP	5.25 mg/dL	EBV anti-EBNA IgG (ELISA)	2
At-lym	2%	Na	142 mEq/L	Anti-CMV IgM (EIA)	0.78
		K	3.2 mEq/L	Anti-CMV IgG (EIA)	64.2
		Cl	105 mEq/L	ANA	(−)
		FPG	89 mg/dL	ASMA	(−)
				M2 Ab	(−)

Ab, antibody; Ag, antigen; ALB, albumin; ALP, alkaline phosphatase; ALT, alanine transferase; ANA, antinuclear antibody; ASMA, anti-smooth muscle antibody; AST, apartate aminotransferase; At-lym, atypical lymphocytes; Baso, basophils; BUN, blood urea nitrogen; Cl, chlorine; CMV, cytomegalovirus; CRE, creatinine; CRP, C-reactive protein; EBNA, Epstein–Barr virus nuclear antigen; EBV, Epstein–Barr virus; Eos, eosinophils; FPG, fasting plasma glucose; γ-GTP, gamma-glutamyl transpeptidase; HA, hepatitis A; Hb, hemoglobin; HBs, hepatitis B surface; HCV, hepatitis C virus; Hct, hematocrit; K, potassium; LDH, lactate dehydrogenase; Lym, lymphocytes; M2 Ab, anti-mitochondria M2 antibody; Meta, metamyelocytes; Mono, monocytes; Na, sodium; P-AMY, pancreatic amylase; Plt, platelet; RBC, red blood cells; Stab, stab neutrophils; T-Bil, total bilirubin; TP, total protein; VCA, virus capsid antigen; WBC, white blood cells.
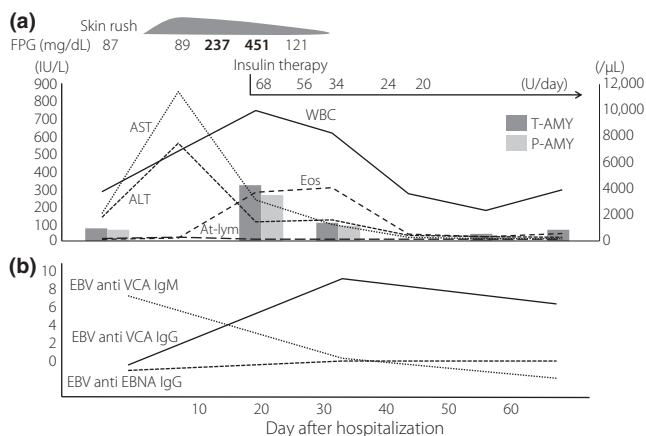

Figure 1 | Clinical course of the hepatobilliary enzymes, fasting blood glucose (FPG), white blood cells (WBC) and Epstein–Barr virus (EBV) antibody titers. (a) A clinical course after admission and (b) the change of EBV antibody titers. AST, aspartate transaminase; ALT, alanine transferase; At-lym, atypical lymphocytes; EBNA, EBV nuclear antigen; Eos, eosinophils; FPG, fasting plasma glucose; IgG, immunoglobulin G; IgM, immunoglobulin M, P-amy, pancreatic amylase; T-amy, total amylase, VCA, viral capsid antigen.

eosinophil count. A biopsy of the affected skin on the 21st hospital day is shown in Figure 2. On the basis of these results, we considered that this systemic erythema was caused by EBV infection. The blood levels of hepatic enzymes remained elevated until the 18th hospital day and began to decrease thereafter; the levels reached the normal range on the 30th hospital day. Anti-EBV nuclear antigen (EBNA) IgG was detected at the start of management. The EBV anti-viral capsid antigen (VCA) immunoglobulin M (IgM) level decreased and the EBV anti-VCA IgG level increased over time. These changes and the clinical course were identical as those observed in the reactivation of EBV infection (Figure 1).

Table 2 shows blood analysis on the 18th hospital day. Abdominal ultrasonography showed no swelling of the pancreas, and arterial blood gas analysis showed metabolic acidosis. Urinalysis was not carried out, but diabetic ketoacidosis was suspected and insulin therapy was initiated immediately. Intensive insulin therapy was carried out, thereby allowing the patient to be discharged on the 65th hospital day. The HbA$_{1c}$ level was 6.4% and its elevation was milder than that of the FPG level. Tests for autoantibodies were negative and the urinary C-peptide level was <2.0 μg/day. Anti glutamic acid decarboxylase (GAD)-Ab was negative in assessments carried out after 3 months and then 1 year. The serum C-peptide level was below the detectable limit both before and after the glucagon load, thereby suggesting an insulin-dependent state. The patient showed no diabetic complications, including retinopathy and nephropathy. These features were identical to those for fulminant type 1 diabetes.

DISCUSSION

In accordance with the diagnostic criteria, this patient was diagnosed with fulminant type 1 diabetes[7]. Human leukocyte antigen (HLA) type sensitivity to type 1 diabetes might be involved in diabetes in Japanese patients, and this relationship is being studied. Some investigators have reported that in patients with type 1A diabetes, HLA-A24 is associated with pancreatic β-cell destruction[8]. Regarding fulminant type 1 diabetes, individuals with DRB1*0405-DQB1*0401 only have been reported to be sensitive to the disease[9], and DRB1*1502-DQB1*0601 and DRB1*1501-DQB1*0602 were negatively associated with type 1A diabetes, but were not protective to fulminant type 1 diabetes[9,10]. In this case, DRB1*1501-DQB1*0602 (known to be protective to type 1A diabetes) were detected. Although the patient did not have DRB1*0405-DQB1*0401 that was considered to be associated with fulminant type 1 diabetes, this case could be considered to be fulminant type 1 diabetes rather than acute-onset type 1 diabetes.

The existing diagnostic criterion for fulminant type 1 diabetes is a high prevalence of flu-like symptoms. Precursive flu-like symptoms are seen in 26.9% of all patients with type 1 diabetes involving an autoimmune mechanism and in a higher percentage (71.7%) of patients with fulminant type 1 diabetes. Viral infection is considered to be an important factor associated with the onset of fulminant type 1 diabetes[6,7,10]. Viruses are
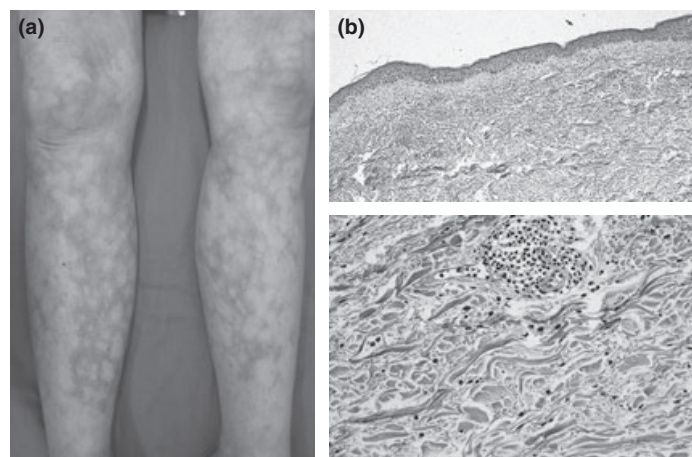
Figure 2 | Clinical and pathological features of the patient. (a) Multi-form erythema in the legs and (b) the lesion gradually changed into livedo. The right upper one indicates edematous change in the upper dermis (hematoxylin–eosin stain; magnification: ×40). The right below one reveals an infiltration by lymphocytes and eosinophils in the dermis (hematoxylin–eosin stain; magnification: ×400).

Table 2 | Laboratory data on 18 days after admission and other examinations related to diabetes mellitus, HLA-DNA typing and viral titers

Hematological analysis		Blood chemistry			
WBC	9940/μL	AST	103 IU/L	BUN	5.9 mg/dL
RBC	245×10^4/μL	ALT	230 IU/L	Cre	0.35 mg/dL
Hb	8.4 g/dL	γ-GTP	468 IU/L	TP	5.2 g/dL
Hct	25.6%	T-Bil	2.7 mg/dL	Alb	2.6 g/dL
Plt	22.8×10^4/μL	ALP	1233 IU/L	CRP	2.62 mg/dL
Stab	7.0%	LDH	402 IU/L	Na	128 mEq/L
Seg	40.0%	CHE	122 IU/L	K	4.9 mEq/L
Lym	12.0%	T-Cho	126 mg/dL	Cl	9.5 mEq/L
Mono	3.0%	TG	93 mg/dL	FPG	451 mg/dL
Eos	37.0%	T-AMY	339 IU/L	HbA_{1c}	6.4 %
Baso	1.0%	P-AMY	279 IU/L		
At-lym	0.0%				
		Arterial blood gas analysis			
		pH	7.328	$PaCO_2$	24.3 mmHg
		PaO_2	111 mmHg	HCO_3	12.4 mmol/L
		BE	−11.7 mmol/L		

Auto-antibody associated islet of the pancreas		Virus titers	
GAD Ab	<0.3 U/mL	HHV-6 IgM	1:10 (−)
IA-2 Ab	<0.4 U/mL	HHV-6 IgG	1:80 (+)
ICA	(−)	HSV-1 IgM (AU)	0.38 (−)
HLA-DNA typing		HSV-1 IgG (AU)	76.9 (+)
HLA-A	A2–A24	VZV IgM (AU)	0.29 (−)
HLA-B	B35–B67	VZV IgG (AU)	14 (+)
HLA-DR	DR15–DR16	Rubella virus IgM (AU)	0.25 (−)
DRB1	1501–1602	Rubella virus IgG (AU)	9.5 (+)
DQB1	0502–0602	Insulin secretion	
DQA1	0102	Urinary C-peptide (24-hour urine collection)	2.0 μg/day
		Serum C-peptide (6 min after glucagon 1 mg loaded)	≤0.03 ng/mL

BE, base excess; CHE, cholinesterase; FPG, fasting plasma glucose; GAD Ab, glutamic acid decarboxylase antibody; HbA_{1c}, hemaglobin A_{1c}; HHV-6, human herpes virus-6; HSV-1, herpes simplex herpes-1; IA-2 Ab, insulin autoimmune-2 antibody; ICA, islet cell antibody; T-amy, total amylase; T-Cho, total cholesterol; TG, triglyceride; VZV, varicella zoster virus.

reported to possibly be associated with the onset of type 1 diabetes[11–13]. Imagawa *et al.*[14] found elevated enterovirus IgA antibody titers in patients with fulminant type 1 diabetes and suggested enteroviruses might play a significant role in the onset of diabetes. A possible relationship between the onset of typical type 1A diabetes and viral infection has been suggested for

several years. A case with possible involvement of EBV at the onset of disease has also been reported. In this case, the HbA$_{1c}$ level was markedly high (15.8%) at onset and the GAD antibody titer rose later, thereby indicating acute-onset disease. This report was published only in Japanese (*Journal of the Japan Diabetes Society* 2003; **46**: 393–397). In our case, EBV anti-VCA IgG and EBV anti-EBNA IgG were already positive at the onset of acute hepatopathy (Figure 1; lower column), thereby suggesting the patient had already been infected with EBV. After the onset of acute hepatopathy, EBV anti-VCA IgM was detected, and this detection was accompanied by an increase in the number of mononucleated cells and the appearance of atypical lymphocytes. These findings suggest that EBV reactivation is responsible for the onset of acute hepatopathy, eruption and fulminant type 1 diabetes. The titers of the other antibodies showed no marked elevations (Table 2). To date, approximately 10 Japanese cases of diabetes with EBV involvement have been reported. However, none of these cases showed the evident course of fulminant type 1 diabetes, and there was no evidence of direct β-cell damage by EBV.

Two possible mechanisms for EBV involvement in the onset of fulminant type 1 diabetes are known; that is, direct injury and influence on immune function. If EBV enters the lytic cycle (proliferation cycle), it produces viral interleukin (IL)-10 (vIL-10)[15]. vIL-10 suppresses the function of helper T1 cells (T$_h$1) and natural killer cells, thereby resulting in suppression of T lymphocyte proliferation and interferon (INF)-gamma and IL-2 formation, leading to a shift in the helper T2 cell (T$_h$2)-predominant immune condition. Many patients also show fulminant type 1 diabetes during pregnancy. Because T$_h$2 is usually predominant during pregnancy, the onset of fulminant-type diabetes during pregnancy indicates disease onset under situations that are unlikely to be associated with autoimmune disease. T$_h$2-predominant immune condition is characterized not only by the absence of likelihood for the onset of autoimmune disease, but also by the reduction of cellular immunity and reduced protection from viral infection. Under T$_h$2 predominance, the host is prone to disorders caused by viral infection, and fulminant type 1 diabetes might develop through an EBV-mediated mechanism of direct pancreatic β-cell destruction.

Chemotherapy for multiple myeloma-induced fulminant type 1 diabetes has not been reported to date, but there are few cases of fulminant type 1 diabetes that developed during steroid therapy. Because the patient had been treated with steroids more than 6 weeks before the onset of diabetes, we thought that the possibility of drug-induced onset of diabetes is considered to be low in this case. The patient seemed to have developed fulminant type 1 diabetes triggered by EBV reactivation during the course of multiple myeloma. No such case has been reported before; therefore, this is a valuable case that deserves reporting. The etiology for fulminant type 1 diabetes involves many unanswered questions, and further studies are required to clarify these aspects.

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