INTERNAL MEDICINE

□ CASE REPORT □

Graves' Disease Associated with Infectious Mononucleosis due to Primary Epstein-Barr Virus Infection: Report of 3 Cases

Hiroshi Akahori[1,2], Yumie Takeshita[1], Reina Saito[1], Shuichi Kaneko[1] and Toshinari Takamura[1]

Abstract

Although the etiology of Graves' disease is still not clear, it is generally suggested that environmental factors such as infections contribute to the development of Graves' disease. We report here three cases of Graves' disease which presented simultaneously with infectious mononucleosis due to primary EBV infection. Acute EBV infection might play an important role in the onset of Graves' disease. These three women complained of a sore throat or neck pain, resembling subacute thyroiditis. In the case of thyrotoxicosis accompanied by sore throat or neck pain, Graves' disease must be distinguished from subacute thyroiditis.

Key words: Graves' disease, hyperthyroidism, Epstein-Barr virus, infectious mononucleosis, atypical cell, liver injury

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Introduction

Graves' disease is a common autoimmune thyroid disorder presenting with hyperthyroidism with various degrees of diffuse goiter and ophthalmopathy (1). Although the etiology of Graves' disease is still not clear, autoantibodies to TSH-receptors (TBII or TSAb) are suggested as playing a causative role in the disease (2). In addition, both genetic and environmental factors are also believed to contribute to the development of Graves' disease (3). Environmental factors include infection with bacterium *Yersinia enterocolitica* (4) or viruses. Among the latter, enterovirus, influenza B virus, retrovirus, and herpesvirus have been previously reported (5-8). However, there have been no reports linking Epstein-Barr virus (EBV) infection with Graves' disease. EBV is a ubiquitous human herpesvirus with worldwide distribution. Primary infection with EBV occurs early in life and typically presents as infectious mononucleosis, which is benign, and most patients recover uneventfully (9). We describe herein three cases of Graves' disease associated with infectious mononucleosis due to primary EBV infection.

Case Report

Case 1

A 20-year-old woman complained of general fatigue, anorexia and right neck pain in September 2006. She was referred to our hospital in October 2006. She was previously healthy and had no family history of autoimmune diseases including Graves' disease and Hashimoto's thyroiditis. She had not received any drugs known to affect thyroid function. On admission, her temperature was 36.4℃, her pulse rate was 96 beats/min and blood pressure was 128/80 mmHg. Her height was 156.0 cm, and her weight was 53.0 kg. She had no change in body weight. Physical examination revealed reddish and swollen tonsils coated with white spots, and lymphadenopathy on right neck. Both lobes of the thyroid gland were slightly enlarged, non-tender, and softly elastic on palpation. Exophthalmos and tremor in the hands were not observed. Laboratory findings are shown in Table 1. White cell count showed leukocytosis with elevated atypical cell count. An inflammation biomarker was not in-

[1]Department of Disease Control and Homeostasis, Kanazawa University Graduate School of Medical Science, Kanazawa and [2]Department of Endocrinology and Metabolism, Tonami General Hospital, Tonami
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Correspondence to Dr. Toshinari Takamura, ttakamura@m-kanazawa.jp

Table 1. Profiles of 3 Patients with Graves' Disease Associated with EB Virus Infection

case number	normal range	1	2	3
age (years)		20	19	19
gender		female	female	female
chief complaints		fatigue, anorexia, right neck pain	sorethroat, nausea, headache, hyperhydrosis, Bw loss	low grade fever, sorethroat, general malaise
period between appearance of thyrotoxic symptoms and onset of infectious mononucleosis (months)		0	1	2
family history of autoimmune diseases		none	maternal grandmother	mother, maternal grandmother
TSH (μIU/mL)	(0.40-4.40)	<0.01	<0.01	<0.01
FT3 (pg/mL)	(2.0-4.9)	22	21.5	14.84
FT4 (ng/dL)	(0.8-1.7)	6.8	6.9	5.71
anti-TSH recepter antibody	(TRAb-human <1.0 IU/L; TBII <10.0 %)	TRAb-human 6.4 (IU/L)	TBII 40.4 (%)	TRAb-human 19.2 (IU/L)
^{99m}Tc uptake on thyroid gland (%)	(0.5-4.0)	8.3	6	4.6
treatment for Graves' disease		MMI 30 mg/day	MMI 30 mg/day	MMI 30 mg/day
WBC (/μL)	(4800-9800)	20200	4800	12160
RBC ($\times 10^4$/μL)	(380-480)	479	431	479
Plts ($\times 10^4$/μL)	(13.0-32.0)	23.6	19.1	21.2
CRP (mg/dL)	(0.00-0.01)	0.16	0.08	0.1
AST (IU/L)	(8-40)	103	82	219
ALT (IU/L)	(5-40)	141	91	300
LDH (IU/L)	(110-220)	478	393	486
ALP (IU/L)	(100-340)	311	269	382
γ-GTP (IU/L)	(0-55)	40	21	52
EB VCA IgM	(< × 10)	× 160	× 20	× 20
EB VCA IgG	(< × 10)	× 1280	× 160	× 640
EB EBNA	(< × 10)	× 10	× 10	× 10
HLA genotyping		DRB1*0405/0803 DQB1*0401/0601	DRB1*0405/1401 DQB1*0401/0503	DRB1*130101 DQB1*0603

creased (CRP 0.16 mg/dL). Liver enzymes were elevated 3 to 4 fold. Chest X-ray and electrocardiographic findings were normal. Ultrasonography of the abdomen confirmed hepatomegaly without splenomegaly. Serological tests were negative for hepatitis C virus, hepatitis B virus, and cytomegalovirus. IgM and IgG antibodies to EBV viral capsid antigen (VCA) were positive, while EBV nuclear antigen (EBNA) was negative. These findings were concordant with the diagnosis of infectious mononucleosis due to primary EBV infection. In addition, thyroid function tests revealed the presence of hyperthyroidism. She had increased serum concentrations of free triiodothyronine (FT3): 22.0 pg/mL (normal range 2.2-4.1 pg/mL) and free thyroxine (FT4): 6.8 ng/dL (normal range 0.8-1.9 ng/dL), although thyroid-stimulating hormone (TSH) was undetectable: <0.4 μIU/mL (normal range 0.4-4.0 μIU/mL). Antibodies to TSH-receptors were positive (TRAb-human 6.4 IU/L). Ultrasonography of the thyroid showed diffuse enlargement of both lobes with heterogenic echogenecity, and increased blood flow by Doppler images (Fig. 1A). The thyroid radioactive ^{99m}Tc uptake was 8.3% (normal range 0.5-4.0%) (Fig. 1B). A diagnosis of Graves' disease was made based on these tests.

Case 2

A 19-year-old woman was admitted for sore throat, nausea, headache and body weight loss in November 2007. She was previously healthy and took no medications. She had been suffering from common cold-like symptoms, such as sorethroat, nausea, and headache, from October 2007. She had palpitations on rest from November 2007 and had a 2 kg-weight loss 2 weeks previously. Her family history included hyperthyroidism in her maternal grandmother. On admission, her temperature was 36.8℃, pulse rate 90 beats/min and blood pressure 98/62 mmHg. Her height was 151.0 cm, weight 45.0 kg. Physical examination revealed bilateral reddish and swollen tonsils without white spots, lymphadenopathy bilaterally on the neck, finger tremor, and prominent eyes with mild lid retraction. Her thyroid was diffusely enlarged, softly elastic, and non-tender on palpation. A cervical bruit was audible. Ultrasonography of the abdomen did not show hepatomegaly or splenomegaly. Laboratory findings are shown in Table 1. White cell count and red cell count were normal, although atypical cell count was elevated. An inflammation biomarker was not increased. Liver enzymes were elevated 2 to 3 fold. Chest X-ray was normal. Electrocardiographic findings showed sinus tachycardia (pulse rate 102 beats/min). On thyroid function tests, she had increased serum concentrations of thyroid hormones (FT 3 21.5 pg/mL and FT4 6.9 ng/dL, TSH was undetectable). Antibodies to TSH-receptors were positive (TBII 40.4%). The thyroid radioactive ^{99m}Tc uptake was 6.0%. A diagnosis of Graves' disease was made based on these tests. At the same time, we found bilateral tonsillitis and liver injury.

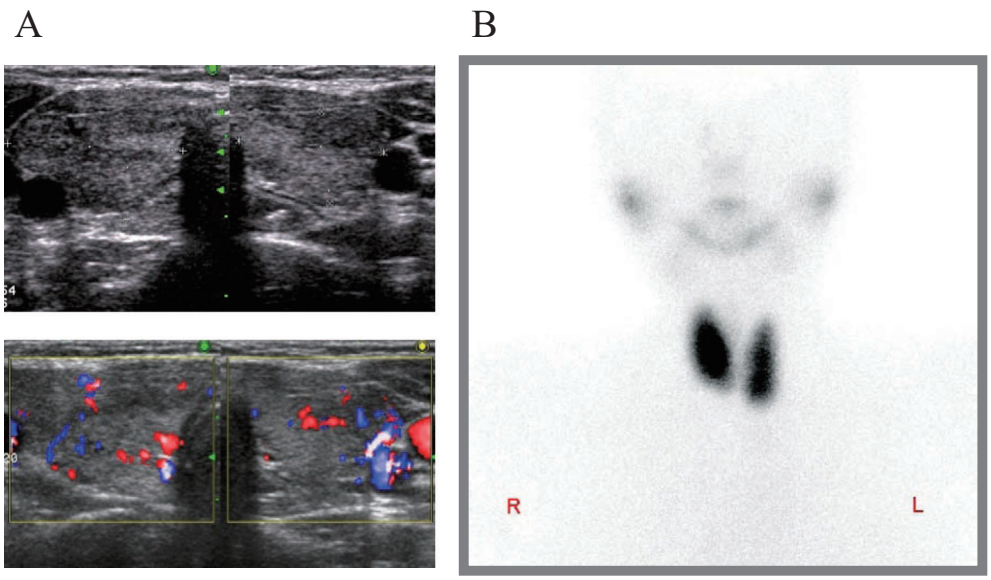

Figure 1. **(A) Thyroid ultrasonography showed diffuse enlargement of both lobes with heterogenic echogenecity. Both lobes showed increased blood flow by Doppler images. (B) Thyroid radioactive ^{99m}Tc uptake was increased without nodular regions.**

IgM and IgG antibodies to EBV VCA were positive, while EBNA were negative. These findings indicated infectious mononucleosis due to primary EBV infection.

Case 3

A 19-year-old woman suffered from low grade fever, sore throat and general malaise in August 2009. She had no remarkable past medical history. Her family history included chronic thyroiditis in her mother, and Graves' disease in her maternal grandmother. On admission, her temperature was 37.6℃, pulse rate 114 beats/min and blood pressure 125/70 mmHg. Her height was 154.0 cm, weight 49.0 kg. She had a 2 kg-weight loss 1 week previously. Physical examination revealed bilateral reddish and swollen tonsils coated with white fur, and lymphadenopathy on bilateral neck. The thyroid was slightly enlarged, softly elastic, and non-tender on palpation. Liver and spleen were impalpable. Laboratory findings are shown in Table 1. Leukocytosis with elevated atypical cell count was observed. An inflammation biomarker was not increased. Liver enzymes were elevated 6 to 7 fold. Serological tests were negative for hepatitis C virus and hepatitis B virus, and IgM antibodies to cytomegalovirus were negative. IgM and IgG antibodies to EBV VCA were positive, while EBNA were negative. Based on these findings, she was diagnosed with infectious mononucleosis due to primary EBV infection. Simultaneously, on thyroid function tests, she had increased serum concentrations of FT 3 (14.84 pg/mL) and FT4 (5.71 ng/dL); TSH was undetectable. Antibodies to TSH-receptors were positive (TRAb-human 19.2 IU/L). The thyroid radioactive ^{99m}Tc uptake was 4.6%. We therefore diagnosed Graves' disease. After the beginning of the treatment to Graves' disease, her liver enzymes gradually decreased and recovered to the normal range as soon as her thyroid hormones normarized.

The clinical findings of these three patients are summarized in Table 1. All of them were diagnosed with infectious mononucleosis due to primary EBV infection concomitantly with Graves' disease, based on clinical laboratory examination, thyroid ultrasonography and scintigraphy. Their human leukocyte antigen (HLA) genotyping showed DRB1*0405/0803 and DQB1*0401/0601, DRB1*0405/1401 and DQB1*0401/0503, DRB1*130101 and DQB1*0603 (Table 1). These patients did not demonstrate susceptibility for Graves' disease. All three patients were treated with methylmercaptoimidazole (MMI) (30 mg/day) and propranolol (30 mg/day). After the beginning of the treatment, they felt very well and their symptoms disappeared. Their liver enzymes gradually decreased. They were discharged a few days later. A few months later, their thyroid hormones recovered to the normal range.

Discussion

Although the etiology of Graves' disease is still incompletely understood, it is generally assumed that the development of Graves' disease is influenced by environmental triggers in genetically susceptible individuals (10, 11). Both genetic and environmental factors are believed to contribute to the development of Graves' disease.

HLA class II molecules, composed of the gene products of three major genes DR, DQ and DP, play a key role in the immune response by binding peptide antigens and presenting them to T cell receptors. These molecules are primary candidates for etiological determinations of Graves' disease because of their involvement in antigen presentation in the periphery and thymic selection, namely, deletion of potentially autoreactive T cells and positive selection of a repertoire of T cells, some of which may be capable of recogniz-

ing self-epitopes and causing autoimmune damage in genetically susceptible individuals (12). HLA class II genes are highly polymorphic. The associations of particular alleles with Graves' disease have been described. In Graves' disease, a positive association of a predisposing role for the DR3 allele and a protective role for the DR5 allele has been found (13, 14). Case-control studies have shown an increased frequency of DRB1*0304, DQB1*02, DQB1*0301/4, and DQA1*0501 in Graves' disease patients, as compared to controls (15-17). HLA haplotype DRB1*0304-DQB1*02-DQA1*0501 is associated with a maximal risk in autoimmune thyrotoxicosis (17). Table 1 summarizes the profiles of our patients. In all three of the present cases, DNA molecular HLA typing did not demonstrate susceptibility for Graves' disease.

The idea that an infection might trigger the development of Graves' disease has long been a popular theory. Infectious agents may induce thyroid autoimmunity by various mechanisms such as inducing alterations and modifications of self-antigens, molecular mimicking between the TSH receptors and viral antigens, and superantigens inducing T-cell activation and inducing expression of HLA molecules on thyroid cells (3). A link between *Yersinia enterocolitica* infection and Graves' disease has already been reported (18, 19). Recently, several studies have suggested that viral infection caused by enterovirus, influenza B virus, retrovirus or herpesvirus may be involved in the pathogenesis of Graves' disease (6, 7, 8, 20). However, an EBV infection causing infectious mononucleosis has not been reported as a triggering factor of Graves' disease.

EBV is well-known to cause many diseases, such as infectious mononucleosis, nasopharyngeal carcinoma, Burkitt lymphoma and Hodgkin's disease. EBV is found worldwide and hides in a latent form in memory B cells in the majority of the world's population. Primary EBV infection during childhood typically entails no or mild symptoms, but in adolescence it often manifests as infectious mononucleosis. EBV remains viable and actively infects the host for life. EBV infection is a continuous source of chronic immune stimulation. Indeed, EBV actively infects B cells and is perpetuated in them (21). EBV has already been reported as being associated with an increased risk of systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and multiple sclerosis (MS). It has been suggested that the titers of anti-EBV antibodies consistent with previous EBV exposure could be high in patients with SLE, RA and MS, and that EBV RNA was found in target organs of these diseases (22-24). These findings indicate that the risk of autoimmune diseases, such as SLE, RA and MS disease, is increased in persons with prior EBV infection. EBV infection is a continuous source of chronic immune stimulation, and may aim an autoimmune process to the thyroid gland. However, the present cases were diagnosed as Graves' disease presenting simultaneously with acute EBV infection by physical and laboratory findings on their initial visit. Although the pathogenesis of EBV infection in the development of Graves' disease is still unclear, an immunopathologic process may be one of the involved mechanisms. As with other viruses, EBV infection causes the production of cytokines such as interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ). These cytokines can induce HLA class II expression and lead to presentation of autoantigens and activation of autoreactive T cells (3). This report is the first to demonstrate the link between EBV infection and Graves' disease. On the other hand, it has been suggested that no differences were observed between patients with Graves' disease and controls in the prevalence of IgG antibodies against EBV (25, 26). The role of EBV infection in the pathogenesis of Graves' disease has is not been fully elucidated. In the present three cases, inflammation itself due to viral infection might be associated with the development of Graves' disease. Further research is needed to clarify the pathogenesis of Graves' disease and to establish a causal link between Graves' disease and EBV infection by investigating the expression of EBV antigen, RNA or DNA in the thyroid tissue, and by prospective observation of Graves' disease associated with EBV infection.

Generally, infectious mononucleosis due to EBV infection can induce upper tract inflammatory symptoms, such as fever, sore throat and neck pain, which resemble subacute thyroiditis. The concomitance of Graves' disease and infectious mononucleosis due to EBV infection may lead to a serious misdiagnosis as subacute thyriditis. Graves' disease must be distinguished from destructive thyroiditis, especially subacute thyroiditis. In the case of thyrotoxicosis accompanied by sore throat or neck pain, testing for antibodies to TSH-receptors and thyroid radioactive ^{123}I or ^{99m}Tc uptake is worthwhile, with a view to differentiate Graves' disease from subacute thyroiditis.

In conclusion, we presented three patients who developed Graves' disease presenting simultaneously with infectious mononucleosis caused by primary EBV infection. These findings suggest that viral infection may play an important role in the development of Graves' disease. When a case of thyrotoxicosis accompanied by sore throat or neck pain is encountered, it is critical to differentiate Graves' disease from subacute thyroiditis, considering the concomitance of Graves' disease and viral infection such as infectious mononucleosis due to primary EBV infection.

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