Human herpesvirus 6 infection mimicking measles: two pediatric cases

Masahide Goto,[1] Hideki Kumagai,[1] Ryou Kawamata,[1] Shizuko Matsumoto,[1] Miki Watanabe,[2] Yasuyuki Nozaki[1]

[1]Department of Pediatrics, Hitachiomiya Saiseikai Hospital, and [2]Department of Viruses, Ibaraki Prefectural Institute of Public Health, Ibaraki, Japan. E-mail: masapon.go@gmail.com or d1305@jichi.ac.jp
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Measles is a highly contagious viral infection associated with clinical symptoms such as fever, cough, conjunctivitis, coryza, eruption and increased serum immunoglobulin M (IgM) antibodies. A clinical diagnosis is easily established when the chain of infection can be followed. However, Japan is currently experiencing sporadic measles outbreaks, which complicate the establishment of diagnosis. Furthermore, other exanthematous infections such as rubella, human parvovirus B19, human herpesvirus 6 (HHV-6) and HHV-7 present with clinical symptoms and IgM antibody levels similar to those in measles. Therefore, real-time polymerase chain reaction virogene testing has been part of Japan's standard diagnostic protocol for measles since 2010. This report presents two pediatric cases clinically resembling measles that were diagnosed as HHV-6 based on a virogene detection test. This underscores the importance of performing pathogen testing to confirm a diagnosis when measles is suspected.

Key words: antibody, children, exanthem subitum, human herpesvirus 6, polymerase chain reaction, World Health Organization.

Measles is a highly contagious viral disease that requires extensive vaccination and surveillance to avoid nationwide epidemics. While its manifestations allow for the establishment of clinical diagnosis, which is usually confirmed by the chain of infection, sporadic outbreaks have been reported in many countries, including Japan. The lack of a chain of infection raises concerns regarding the accuracy of clinical diagnosis alone.

Outbreaks of measles have been on the rise since 2009, particularly in the regions of Africa, South-East Asia and Europe[1]. Therefore, it is globally imperative to extend measles vaccination coverage and reduce measles-related deaths. All six World Health Organization (WHO) regions have committed to measles elimination by setting specific target dates. The WHO region of the Americas achieved this goal in 2002; the European, Eastern Mediterranean, Western Pacific and African regions aim to eliminate measles by the end of 2015 and the South-East Asia region by 2020[2]. Inclusion of an enzyme-linked immunosorbent assay (ELISA) and serum immunoglobulin M (IgM) tests as standard diagnostic protocols is recommended[3]. However, other exanthematous infections, such as rubella, infectious erythema [human parvovirus B19 (HPV B19)] and exanthem subitum [human herpesvirus 6 (HHV-6) and HHV-7], also present with increased circulating measles-specific IgM antibodies[4-6]. Therefore, in 2010, Japan adopted the real-time polymerase chain reaction (PCR) virogene detection test as an integral part of the standard diagnostic protocol. This report describes two pediatric patients who displayed clinical symptoms and increased IgM antibody levels consistent with measles infection, but were diagnosed with HHV-6 infection based on serum virogene testing. All clinical materials used in this study were obtained for diagnostic purposes, with informed consent obtained from the parents of the children.

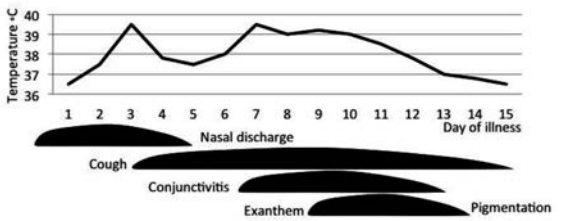

Fig. 1. Clinical course of case 1. The patient presented with fever, nasal discharge, cough, conjunctivitis and transient exanthem leaving dark pigmentation.

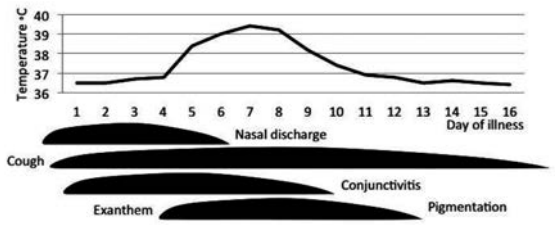

Fig. 2. Clinical course of case 2. The patient presented with fever, nasal discharge, cough, conjunctivitis and transient exanthem leaving dark pigmentation.

Case Reports

Case 1

A previously healthy, immunocompetent 3-year-old boy with no exanthem subitum received the measles-rubella (MR) vaccine at 1 year of age. He subsequently developed fever, cough and nasal discharge. His fever decreased temporarily but returned the following day. Furthermore, he developed conjunctivitis with eye discharge in addition to full-body exanthem and severe cough. Physical findings included bulbar conjunctival hyperemia and pharyngeal erythema; no Koplik's spots were noted in the mouth. Serum levels of measles IgM antibody were measured by enzyme immunoassay (EIA) (Denka Seiken Co., Ltd., Tokyo, Japan: sensitivity 97.5%, specificity 100%) and determined to be 2.53 EIA values, which supported a diagnosis of modified measles. The fused erythematous macules disappeared, leaving residual pigmentation (Fig. 1). Although several immunoassays were conducted to verify this diagnosis, the measles gene was not observed in serum, throat swabs or urine samples (Table I). Real-time PCR and nested PCR (ABI PRISM 7500 HT Sequence Detection System; Applied Biosystems, Foster City, CA, USA) were performed to detect the following panel of viruses: rubella, HPV B19, HHV-6 and HHV-7 (Table II). The results were positive only for HHV-6 (variant B). Markedly increased HHV-6-specific antibodies were detected by a fluorescent antibody (FA) assay. Consequently, the patient was diagnosed with HHV-6 infection based on the combination of gene detection and increased antibody levels.

Case 2

A previously healthy, immunocompetent 2-year-old boy with no exanthem subitum received the MR vaccine at 1 year of age. He subsequently developed fever, cough and nasal discharge, followed by conjunctival hyperemia and rash (Fig. 2). His measles IgM antibody levels increased fivefold from the acute to the convalescent phase. Based on these results, the subject was diagnosed with modified measles. Nevertheless, a virogene detection test was performed to detect measles virus, rubella virus, HPV B19, HHV-6 and HHV-7, which was positive only for HHV-6 (variant B) (Table I). The diagnosis of HHV-6 infection was confirmed by an FA assay, which demonstrated increased HHV-6 antibody levels.

Discussion

We have described two pediatric cases of HHV-6 infection that presented with both measles-like clinical symptoms and changes in measles antibody levels. These slight elevations in measles IgM antibody levels led to misdiagnoses. However, these diagnoses were reevaluated when the measles gene was not detected during the measles virus shedding period. HHV-6 is shed in the saliva at high levels for 12 months[7] following the onset of infection, after which it is intermittently excreted. HHV-6 was detected repeatedly in our cases; however, the diagnoses for these patients were confirmed by the absence of history suggestive of typical exanthem subitum, repeated gene detection and markedly increased HHV-6 antibody levels.

Primary HHV-6 infection frequently induces exanthem subitum[8]. Two earlier studies have reported the occurrence of transient exanthem in 24%[7] and 30%–60%[9] of HHV-6-infected patients. A prospective cohort study on HHV-6 infection reported symptoms of fever, irritability, nasal discharge, cough, diarrhea and vomiting in a significant number of cases[8]. In addition, cases of HHV-6 infection confirmed by paired sera antibody titers revealed that 21% had symptoms

Table I. Viral Antibody Levels and Gene Identification of the Two Cases

		Measles					HHV-6		
		EIA		PA (Titer)	HI (Titer)	Gene	FA (Titer)		Gene
		IgM	IgG				IgM	IgG	
Case 1	Day 7	<0.8	20.5	1024	16	Negative	10	<10	Positive
	Day 14	2.53	60.5	2048	32	Negative	20	320	Positive
Case 2	Day 8	0.55	67.9	2048	NA	Negative	<10	<10	Positive
	Day 12	2.89	90.4	2048	32	Negative	20	320	Positive

EIA, Enzyme immunoassay; FA, Fluorescent antibody test; HI, Hemagglutination inhibition test; NA, not available; PA, Particle agglutination assay.
The IgM and IgG antibody cutoff levels by EIA were 0.8 and 2.0, the equivocal ranges 0.8–1.2 and 2.0–3.9, and positive 1.2 and ≥4.0, respectively. The cutoff levels by PA, HI and FA were 16, 8 and 10 titers, respectively.

Table II. Oligonucleotides and TaqMan Probes for the Real-Time and Nested PCR Assays

Target virus		Primer / Probe	Oligonucleotide sequence 5′ → 3′
Measles		Forward primer	CASRGTGATCAAARTGRRARYGAGCT
		Reverse primer	YCCTGCCATGGYYTGCA
		TaqMan Probe	(6-FAM) TCYGATRCAGTRTCAAT (MGB)
HHV-6		Forward primer	CAAAGCCAAATTATCCAGAGCG
		Reverse primer	CGCTAGGTTGAGAATGATCGA
		TaqMan Probe	(6-FAM) CACCAGACGTCACACCCGAAGGAAT (MGB)
HHV-7		Forward primer	ATGTACCAATACGGTCCCACTTG
		Reverse primer	AGAGCTTGCGTTGTGCATGTT
		TaqMan Probe	(6-FAM) CACGGCAATAACTCTAG (MGB)
Rubella	Outer	Forward primer	TCCTTGCGCCGAAGACT
		Reverse primer	AGAGGGGGTCCACTTGAG
	Inner	Forward primer	CCACTGAGACCGGCTGCG
		Reverse primer	GCCTCGGGGAGGAAGATGAC
HPV B19	Outer	Forward primer	CACTATGAAAACTGGGCAATAAAC
		Reverse primer	AATGATTCTCCTGAACTGGTCC
	Inner	Forward primer	ATAAACTACACTTTTGATTTCCCTG
		Reverse primer	TCTCCTGAACTGGTCCCG

HHV-6, human herpesvirus 6; HHV-7, human herpesvirus 7; HPV B19, human parvovirus B19; FAM, 6-carboxyfluorescein; MGB, minor groove binder
The real-time PCR assay was performed for measles virus, HHV-6 and HHV-7. The nested PCR assay was performed for rubella virus and HPV B19.

typical of exanthem subitum, but 73% and 46% of cases fulfilled the clinical diagnostic criteria for measles and rubella, respectively[10]. These results suggest that HHV-6 causes more varied symptoms than originally thought, thus leading to difficulties in establishing a diagnosis of either measles or HHV-6 infection based on clinical findings alone.

A prompt and precise diagnosis of measles is mandatory from both public health and clinical

practice perspectives. WHO recommends EIA as the standard diagnostic test for measles-specific IgM antibodies because it does not involve specialized equipment or complicated techniques[3]. Measles IgM antibody levels are known to increase in certain exanthematous infections (caused by rubella virus, HPV B19 and HHV-6)[4-6], as demonstrated in our cases. Thus, even with slightly elevated measles-specific IgM antibody levels, the possibility of false positives must be considered. Thus, it is difficult to distinguish among these exanthematous diseases based on antibody testing because they are often very similar clinically.

Widespread use of the MR vaccine in Japan has raised concerns regarding diagnosis based solely on clinical symptoms and antibody levels. Therefore, real-time PCR virogene testing has been the standard procedure in Japan since 2010 because of its rapidity of detection, very high sensitivity during the early stages of infection and capability of identifying the virus genotype to detect imported strains. Thus, if measles is clinically suspected, throat swabs and blood and urine samples should be submitted to a local public health laboratory for definitive diagnosis by real-time PCR virogene testing. This surveillance system has now become effective in Japan[11,12]. Laboratories are encouraged to perform sequencing and genotyping and submit the sequencing information to the WHO genotype database[13].

In conclusion, in cases where measles is suspected when patients present with exanthematous disease(s) accompanied by fever, it is important to perform pathogen diagnosis in addition to standard diagnostic tests.

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