ORIGINAL ARTICLE

Infectious Mononucleosis-Like Syndrome Due to Human Herpesvirus-6 : A Report of Five Cases

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Summary

The syndrome of infectious mononucleosis classically refers to the triad of fever, pharyngitis and adenopathy. This is supported by laboratory findings of absolute lymphocytosis in which more than 10% of the lymphocytes are atypical and a positive heterophile antibody test[1]. We report 5 patients seen at the Assunta Hospital, Petaling Jaya, between late September 1995 and December 1995, with infectious mononucleosis-like syndrome due to Human Herpesvirus-6. The clinical presentations of these 5 patients resemble that of the classical infectious mononucleosis due to Epstein-Barr virus. The diagnosis can only be differentiated by laboratory investigations.

Key Words: Human Herpesvirus-6, Mononucleosis-like syndrome

Introduction

The description and epidemiology of infectious mononucleosis was well documented in the early nineteenth century[1] before the recognition of Epstein-Barr virus (EBV) as its dominant cause in 1967[2]. In developing countries, like Malaysia, EBV infection occurs very early in life with almost 100% of the population being seroconverted[3] by early childhood. Hence, infectious mononucleosis-like illnesses should rarely be due to EBV infection for children above 3 years. Though it is often mentioned that Human Cytomegalovirus (CMV), Human Immunodeficiency virus (HIV) and *Toxoplasma gondii* infections can lead to mononucleosis-like illness, the newly isolated member of the human herpes virus family, Human Herpesvirus-6 (HHV-6)[4] could be a more likely pathogen in this region. We present 5 children seen at the Assunta Hospital, Petaling Jaya, between late September 1995 and December 1995, having mononucleosis-like illness due to HHV-6.

Materials and Methods

This is a prospective collaborative study between the Paediatric Unit, Assunta Hospital, Petaling Jaya and the Department of Medical Microbiology, University of Malaya, Kuala Lumpur, between September and December, 1995. The patients selected in this study presented with fever, pharyngitis with tonsillar exudates, cervical lymphadenopathy, and absolute lymphocytosis with increased atypical lymphocytes.

The laboratory investigations done to establish the aetiological agent of the mononucleosis are:-

1. *Streptococcus pyogenes* – Bacteriological culture of throat swab and anti-streptolysin O titre (ASOT) for both acute and convalescence sera.

2. EBV – Monospot test for the heterophil antibody.
   – VCA-IgM and VCA-IgG for both acute and convalescence sera by commercial ELISA kit.

3. CMV – IgM and IgG for both acute and convalescence sera by commercial ELISA kit.

4. HHV-6 – IgM and IgG for both acute and convalescence sera by commercial indirect immunofluorescence test kit.
   – Detection of HHV-6 antigen on the patient's leucocytes.

The acute blood specimens were taken at the time of clinical diagnosis. The convalescence blood specimens were taken 2 to 3 weeks later. Both the acute and convalescence sera were subjected to IgM and IgG testing for CMV, EBV and HHV-6 to highlight potential cross-reactivity of the antisera. During the acute phase, leucocytes were harvested using the Ficoll-Hypaque technique and cultured in RPMI growth medium supplemented with 10% fetal calf serum, interleukin-2 (10 iu/ml), phytohaemagglutinin (10μg/ml) and incubated at 37°C with 5% carbon dioxide. After 10 to 15 days of self-culture, the leucocytes were spinned down at 2000 rpm to remove the culture medium. The leucocytes were then washed once with phosphate buffer saline (PBS) and resuspended in 0.5ml of PBS. 50μl of the leucocytes suspension was transfered on to each of the 10-wells teflon coated slide and dried over heated plate. The dried leucocytes on the teflon coated slide were subsequently fixed for 10 minutes in cold acetone. The detection of HHV-6 antigen was carried out by indirect immunofluorescence test using monoclonal antibody against HHV-6 p150 protein.

Results

The clinical features and laboratory findings of the 5 patients are summarized in Tables I and II.

Table I
Clinical features of 5 children with mononucleosis-like illness

Name	CCW	TSS	TCP	GV	LFW
Age (years)	3.25	8	3.25	3.25	2.25
Sex	M^	F^	M	M	M
Symptoms					
Duration of fever (days)	10	10	13	9	15
Neck swelling	++	++	+++	++	+++
Stridor	–	–	+	–	+
Hoarseness of voice	+	–	+	+	+
Signs					
Bilateral cervical lymphadenopathy#	+++	+++	+++	+++	+++
Tonsils	GE*	GE	GE	GE	GE
Tonsillar exudates	++	++	+	++	++
Periorbital swelling	+	±	++	+	++
Rashes	–	–	–	–	–
Hepatomegaly	2.5 cm	–	3 cm	–	–
Splenomegaly	–	–	3 cm	–	–

GE = grossly enlarged M^ = male F^ = Female*
– = Absent ± = Equivocal + = Present
++ = Obvious +++ = Prominent
 # The cervical lymph nodes ranged from 2 cm to 3 cm in size

Table II
Laboratory profiles of 5 children with mononucleosis-like syndrome

Name		CCW	TSS	TCP	GV	LFW
Haematology						
Total white (TW) x 10^9/L		18.6	17.5	24.8	17	12.4
Lymphocyte (% of TW)		42	38	49	41	36
Atypical lymphocyte (% of TW)		8	46	13	15	8
Platelet x 10^9/L		130	240	322	284	336
Clinical chemistry						
SGPT (8-54 i.u./L)		ND	ND	ND	normal	122
SGOT (16-40 i.u./L)		ND	ND	ND	normal	74
Bacteriology						
Throat swab culture		NS	ND	NS	NS	NS
Serology						
Monospot	acute	–	–	–	–	–
	convalescence	–	–	–	–	–
CMV- IgM	acute	±	+	–	+	+
(ELISA)	convalescence	–	–	–	–	–
IgG	acute	–	+	–	–	–
	convalescence	–	+	–	–	–
EBV- IgM	acute	–	–	–	–	–
(ELISA)	convalescence	–	–	–	–	–
IgG	acute	+	+	+	+	+
	convalescence	+	+	+	+	+
HHV-6-IgM	acute	+	+	+	+	+
(ELISA)	convalescence	+	+	+	+	+
IgG	acute	1/1280	1/1280	1/320	1/320	1/640
	convalescence	1/5120	1/2560	1/1280	1/640	1/1280
HHV-6 antigen detected on cultured leucocytes (IFT)		+	+	+	+	+
ASOT		NS	NS	NS	NS	NS

ND = Not done *NS = Not significant* *+ = Detected*
± = Equivocal *ELISA = Enzyme-linked Immunosorbent Assay* *IFT = Indirect Immunofluorescence Test*
ASOT = Anti-streptolysin 'O' Titre

Table I shows the presentation of the 5 patients having mononucleosis-like illness. The prominent clinical features in all the 5 children are swinging fever of 9 to 15 days, obvious cervical lymphadenopathy (Fig. 1) and grossly enlarged tonsils with white exudates (Fig. 2). These findings correspond to the classical mononucleosis illness of EBV. The clinical diagnosis of mononucleosis-like syndrome in the patients was supported by an increase in the absolute lymphocyte count with more than 10% of atypical lymphocytes (Table II). Periorbital swelling which was noticed and could be confused with post-streptococcal acute glomerulonephritis was excluded by bacterial culture of throat swabs and ASOT.

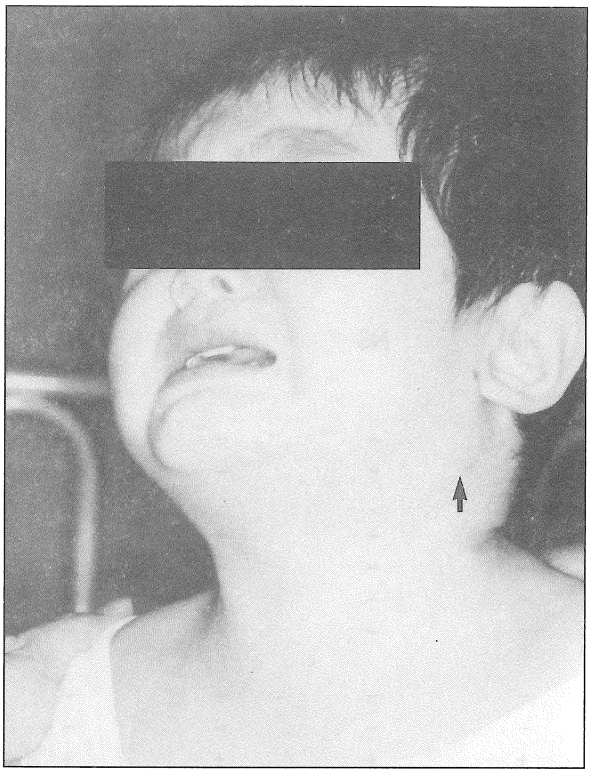

Fig. 1: Neck swelling due to prominent enlarged cervical lymph nodes on one of the patients

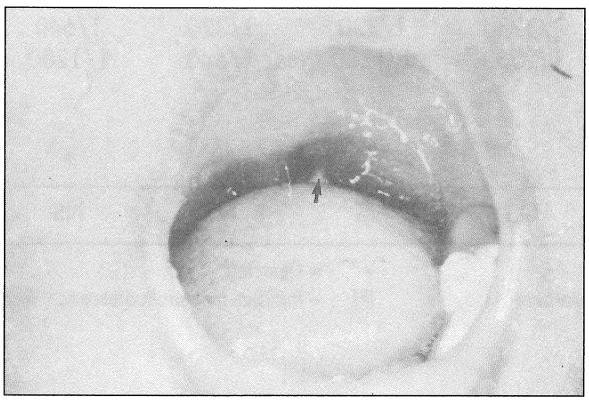

Fig. 2: Pharynx of a patient showing enlarged tonsils with white exudate

Discussion and Conclusion

Classically, infectious mononucleosis (IM) refers to an EBV induced illness in young adults associated with characteristic swing fever, exudative tonsillar pharyngitis, prominent cervical lymphadenopathy, reactive lymphocytosis and serologically detectable heterophil antibodies. The presented 5 patients have all the clinical features as described except for the negative monospot test. More than 10% of the IM due to EBV are heterophil antibody negative and the final diagnosis of the aetiology of the mononucleosis illness was based on:-

i) negative test for EBV specific VCA-IgM
ii) positive test for HHV-6 specific IgM and
iii) detection of HHV-6 specific antigen on the lymphocytes after 14 to 15 days of culture.

Not all the patients showed a four-fold rise in specific HHV-6 IgG titres probably because the IgG titres could have reached the plateau level when seen at the hospital. Three of the patients had positive CMV IgM antibody reactivity on the acute sera but were negative from the convelescence sera (Table II). This could be due to cross-reactivity of the antibody response. None of the patients had the maculopapular rash as described in exanthem subitum. In short, there is no sure way of differentiating mononucleosis illness of HHV-6 from EBV clinically, unless supported by specific laboratory investigations. Furthermore, in a developing country like Malaysia, almost 100% of the population has already EBV seroconverted by the age of 3 years[3]. We therefore suggest that in our population HHV-6 could be a more important pathogen in mononucleosis-like illness in children above 3 years old, especially if the monospot test and specific EBV-VCA IgM antibodies are negative.

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