Human Herpesvirus 6 Infection Associated with Hemophagocytic Syndrome

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Table 1. Serological studies

Virus-associated hemophagocytic syndrome (VAHS), first described by Risdall et al. [1], is a potentially self-limited proliferation of cytologically benign histiocytes exhibiting marked hemophagocytosis, in association with a systemic viral infection. Thus far, Epstein-Barr virus, cytomegalovirus, herpes simplex virus and adenovirus have been known as the most common causative agents [2-4]. We describe a girl who had VAHS associated with human herpesvirus 6 (HHV-6) infection.

A 15-year-old girl, previously well, complained about common-cold-like symptoms, a sore throat, malaise and had otitis media in April 1993. Several days later, she was referred to our hospital because of fever and for evaluation of leukopenia. Physical examination revealed pharyngitis and slightly enlarged and tender cervical lymph nodes. An enlarged liver extending 1 cm below the right costal margin was palpated but no splenomegaly was found. The blood count revealed: Hb 13.2 g/dl, platelet count $115 \times 10^9/l$ and WBC $0.5 \times 10^9/l$ (band 14%, segmented neutrophils 35%, monocytes 6%, lymphocytes 45%). The CD4⁺/CD8⁺ ratio was 0.68. Bone marrow aspiration from the iliac crest revealed normal cellularity (total nuclear cells, $169 \times 10^9/l$) with a normal megakaryocyte count ($0.09 \times 10^9/l$) and profuse macrophage infiltration (4.5 %) with evidence of hemophagocytosis. The coagulation screen was within normal limits. The serum lactate dehydrogenase (LDH) level was 1,097 WU (normal range: 185-330 WU), ferritin 0.631 g/l (normal range: 0.003-0.078 g/l) and total cholesterol and triglycerides were within the normal range. On serological examination, the titers of anti-HHV-6 IgM were 40 and 10 in the first and the second measurement, respectively and those of IgG were 10 and 10. The HHV-6 antibody was evaluated using the indirect immunofluorescence method as described previously [5]. Serum specimens that showed fluorescence at a 10-fold dilution were considered positive for HHV-6 antibody. During the clinical course, the titer of IgM decreased to less than 10 while that of IgG increased to 80 (table 1). These findings suggested that she had a recent HHV-6 infection. However, HHV-6 DNA could not be detected in the cultures of mononuclear cells (obtained on May 20, 1993) or in the serum (sample from June 12, 1993). No evidence of

Titers of anti-HHV-6

WBC

$\times 10^9/l$

Platelets $\times 10^9/l$

$\frac{1}{8}G$

IgM

May 2, 1993	NT	NT	0.5(49)	115
June 12, 1993	40	10	1.4(26)	179
August 25, 1993		10	10	2.6(51)
December 22, 1993		10	20	3.0(31)
April 5, 1994	<10	80	3.5(46)	254

Figures in parentheses represent percentage of neutrophils. NT = Not tested.

recent infections with other viruses (Epstein-Barr virus, human herpesvirus, cytomegalovirus and adenovirus) could be found serologically. Bacterial and fungal infections were also excluded by negative cultures of the blood and urine. A diagnosis of VAHS following HHV-6 infection was made and she was followed without therapy. On May 12, therapy with prednisolone (1 mg/kg) was begun as no improvement was obtained in the clinical condition or the laboratory data. Soon she became afebrile, and the WBC count gradually increased to $2.5 \times 10^9/l$, a week after the beginning of the prednisolone therapy. After prednisolone therapy for 1 month, the fever and the other clinical manifestations were well controlled but the WBC count again decreased. At present she is in a good condition except for cervical lymphadenopathy. The WBC count has gradually improved though it is still below normal.

In our search of the literature, we found one report of VAHS following HHV-6 infection [6].

Usually, HHV-6 infection results in exanthema subitum in children. Our patient had not been noticed to have exanthema subitum in infancy. All herpesviruses have been shown to be associated with VAHS [7] and thus, HHV-6 could also induce

this disease. Several reports suggest that this virus infection may also be associated with histiocytic necrotizing lymphadenitis (Kikuchi's disease), which mainly affects adolescents and causes swelling of the cervical lymph nodes, leukopenia and an elevation of LDH [8], but does not cause hepatosplenomegaly or thrombocytopenia, which are often observed in VAHS. However, a case of Kikuchi's disease associated with findings of hemophagocytosis in the bone marrow was recently reported [9]. The roles of HHV-6 in these two diseases should be examined further in more detail.

In conclusion, we diagnosed our patient as having VAHS associated with HHV-6 infection on the basis of laboratory findings (serological titers, thrombocytopenia, and hemophagocytosis in the bone marrow) and because the cervical lymph nodes were too small for Kikuchi's disease.

Acknowledgment

We thank Mrs Masako Saitoh and Miss Yasuko Nonaka for the assay of the lymphocyte subsets.

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