

Detection of human herpes virus 6 (HHV 6) in the skin of a patient with primary HHV 6 infection and erythroderma

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Abstract

Human herpes virus 6 (HHV 6) has been implicated as the causative agent of exanthema subitum in young children. Recently, we reported two cases of a severe, infectious, mononucleosis-like syndrome resulting from a primary HHV 6 infection in immunocompetent adults. Both of these patients had the skin condition generally referred to as "erythroderma". A skin-biopsy specimen from one of them, a 43 year old man, was examined. Using immunohistochemical staining and in situ hybridisation, lymphocytes infected with HHV 6 were found in the skin.

It is proposed that the erythroderma in immunocompetent adults infected with primary HHV 6 is provoked by infiltration of infected inflammatory cells or infected neoplastic lymphocytes into the dermis.

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Human herpes virus 6 (HHV 6) is a distinct new member of the herpes virus group.^{1,2} Yamanishi *et al* identified it as a causative agent for exanthema subitum,³ but the natural history of HHV 6 infection and the spectrum of related diseases are still unclear. We recently reported two cases of a

fulminant, infectious, mononucleosis-like syndrome resulting from a primary HHV 6 infection in immunocompetent adults.^{4,5} Acute, diffuse "erythroderma" was the most striking feature of both cases.

Case report

A 43 year old man was admitted to hospital with a seven day history of fever and a five day history of progressive, generalised skin eruption. He had high fever (over 40°C), bilateral cervical lymphadenopathy, mild splenomegaly, generalised skin rash with exfoliation, leucocytosis ($16.9 \times 10^9/l$ with 58% atypical lymphocytes), and liver dysfunction (aspartate aminotransferase 271 IU/l, alanine aminotransferase 391 IU/l, lactate dehydrogenase 2067 IU/l). The detailed clinical and laboratory findings have been reported before.⁵ Using PCR, we amplified HHV 6 DNA from peripheral lymphocytes and the skin biopsy specimen. We also sought HHV 6 antigen in peripheral CD4+ lymphocytes by using HHV 6 specific monoclonal antibody.

Methods

We examined a skin biopsy specimen for HHV 6 infection, using the avidin biotin alkaline phosphatase method with HHV 6 specific monoclonal antibodies OHV-1 and OHV-2 (kindly provided by Dr Yamanishi, Osaka University, Osaka, Japan).⁶ In situ hybridisation was performed with ³⁵S-labelled HHV 6 DNA probe (*Pst* I fragment from the *Bam* HI site).⁷ Lymphocytes which had infiltrated into the skin biopsy specimen were studied immunohistochemically, using the avidin-biotin alkaline phosphatase method with a broad panel of monoclonal antibodies. The antibodies applied to the paraffin wax embedded sections were L-26 (CD20), Kp-1 (CD68), UCHL-1 (CD45RO), and T3 (CD3). Those applied to the frozen sections comprised OKT6 (CD1a), OKT11 (CD2), Leu4 (CD3), OKT4 (CD4), OKT8 (CD8), B4 (CD19), B1 (CD20), Tac (CD25), and Ki-67. Double staining was also performed on the frozen sections using Ki-67 with CD4, Ki-67 with CD8, and Ki-67 with CD20.

Results

The infiltrating lymphocytes in the dermis were positive for UCHL-1 (CD45RO), T3 (CD3), OPD-4 (CD4), OKT11 (CD2), Leu4 (CD3), OKT4 (CD4), OKT8 (CD8), and

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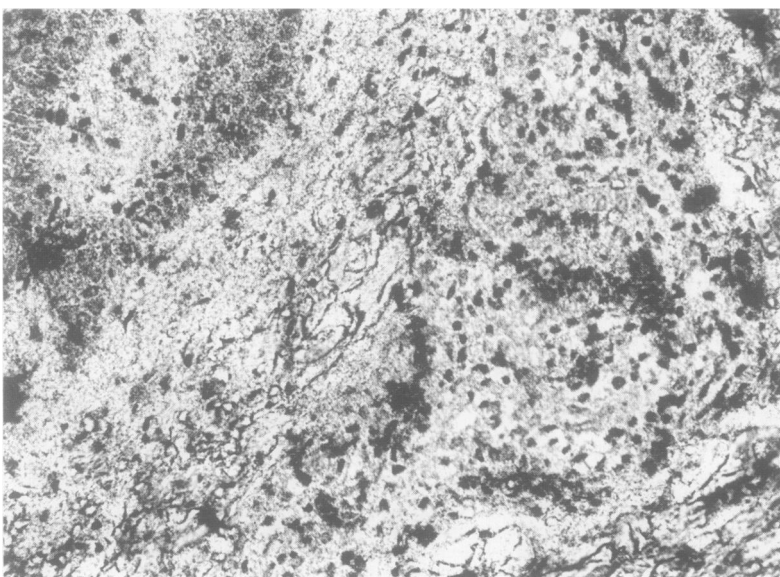


Figure 1 In situ hybridisation for herpes virus 6 DNA in the skin biopsy specimen using an ³⁵S-labelled HHV 6 DNA probe. Numerous grain deposits can be seen in a considerable number of infiltrating lymphocytes.

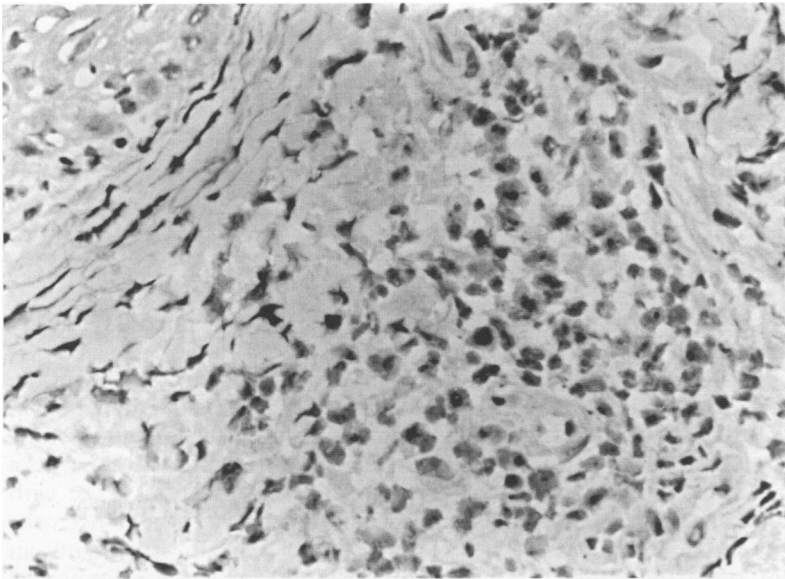


Figure 2 HHV 6 antigen staining of the same specimen. Numerous OHV-2 positive lymphocytes can be seen.

Leu11 (CD16). The CD4+ cells had larger nuclei than the CD8+ cells, and the CD4+ lymphocytes were positive for Ki-67.

With in situ hybridisation using ³⁵S-labelled HHV 6 DNA, numerous grain deposits could be seen in some infiltrating lymphocytes in the dermis (fig 1). HHV 6 antigen staining of the same skin specimen showed numerous OHV-1 or OHV-2 positive lymphocytes (fig 2) in the dermis, particularly around the hair follicles or vessels.

Discussion

In previous reports of a severe, infectious, mononucleosis-like syndrome arising from a primary HHV 6 infection in immunocompetent adults, an acute, diffuse, "erythroderma" was one of the most striking features.^{4,5} Successful detection of HHV 6 DNA using the polymerase chain reaction in the skin biopsy specimen led us to attempt to identify the HHV 6 infected cell population in the skin. We performed in situ hybridisation of HHV 6 DNA with ³⁵S-labelled HHV 6 probe (*Pst* I fragment from the *Bam* HI site), and immunohistochemical staining with the HHV 6 specific monoclonal antibodies OHV-1 and OHV-2, using the avidin-biotin alkaline phosphatase method in the same skin biopsy specimen.

Aggressive infiltration of CD4+ and CD8+ T cells was evident in the dermis and HHV 6 DNA was detected in a considerable number of infiltrating lymphocytes (fig 1A). Furthermore, many infiltrating lymphocytes were positive for both OHV-1 and OHV-2 (fig 2B). Because HHV 6 antigen was detected in CD4+, but not CD8+, T cells in circulation,⁵ these HHV 6 infected lymphocytes were probably CD4+ T cells.

The erythroderma appeared after a five day history of fever and became concurrent with an infectious mononucleosis-like illness which healed with abundant exfoliation. The skin lesion was much more severe than that in exanthema subitum caused by HHV 6. A similar acute erythroderma was observed in another patient with HHV 6 induced, severe, infectious mononucleosis who was reported to have fulminant hepatitis with severe atypical lymphocytosis also probably resulting from the primary HHV 6 infection.⁸

Erythroderma or generalised exfoliative dermatitis is not usually seen in infections caused by other viruses. It has been shown to arise from an infiltration of inflammatory cells or neoplastic lymphocytes, such as Sézary cells, into the dermis. Accordingly, acute erythroderma in our case could be ascribed to the unregulated inflammatory response of CD8+ T cells against HHV 6 infected CD4+ T cells in the dermis. This finding may be a feature peculiar to a primary HHV 6 infection in immunocompetent patients.

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