

4.3 Further Reading

Bertram G, Dreiner N, Krueger GR, Ramon A, Ablashi DV, Salahuddin SZ, Balachandran N. Frequent double infection with Epstein-Barr virus and human herpesvirus-6 in patients with acute infectious mononucleosis. *In Vivo* 5: 271-279, 1991

Hall CB, Long CE, Schnabel KC, Caserta MT, McIntire KM, Costanzo MA, Knott A, Dewhurst S, Insel RA, Epstein LG. Human herpesvirus-6 infection in children. A prospective study of complications and reactivation. *N Engl J Med* 331: 432-438, 1994

Wiersbitzky S, Ratzmann GW, Brims R, Wiersbitzky H. Reactivation in children of juvenile chronic arthritis and iridocyclitis associated with human herpesvirus-6. *Paediatr Grenzgeb* 31: 203-205, 1993

Descamps V, Valance A, Edlinger C, Fillet AM, Grossin M, Lebrun-Vignes B, Belaich S, Crickx B. Association of human herpesvirus 6 infection with drug reaction with eosinophilia and systemic symptoms. *Arch Dermatol* 137: 301-304, 2001

Wagner M, Krueger GRF, Ablashi DV, Whitman JE. Chronic fatigue syndrome (CFS): A critical evaluation of testing for active human herpesvirus-6 (HHV-6) infection: Review of data from 107 cases. *J Chron Fatigue Syndr* 2: 3-16, 1996

Review article:

Krueger GRF, Ablashi DV. Human herpesvirus-6: A short review of its biological behavior. *Intervirology* 46: 257-269, 2003

5. CARDIOVASCULAR SYSTEM

5.1 Introduction

Cardiovascular symptoms and respective pathological changes have been reported occasionally in active HHV-6 infections. A comprehensive review was published by Max Buja (2006). HHV-6 frequently appears to reside in vascular endothelial cells, and viral DNA has also been extracted from myocardial tissue. The various cardiovascular lesions found in association with active HHV-6 infection are summarized in Table 2.

Pathologic Entity	Patient	Immune Status	HHV-6 Testing
Myocarditis	adult, child	nl, AIDS, cardiac allograft	serology, PCR (myocardium)
Dilated cardiomyopathy	adults	nl	serology, PCR (myocardium)
L. ventricular dysfunction	adults	nl	serology, EMB PCR
Large vessel arteritis	child	nl	serology, PCR (tissue)
Thrombotic microangiopathy	adult	BMTx	serology
Kawasaki's disease	adult	nl	serology J

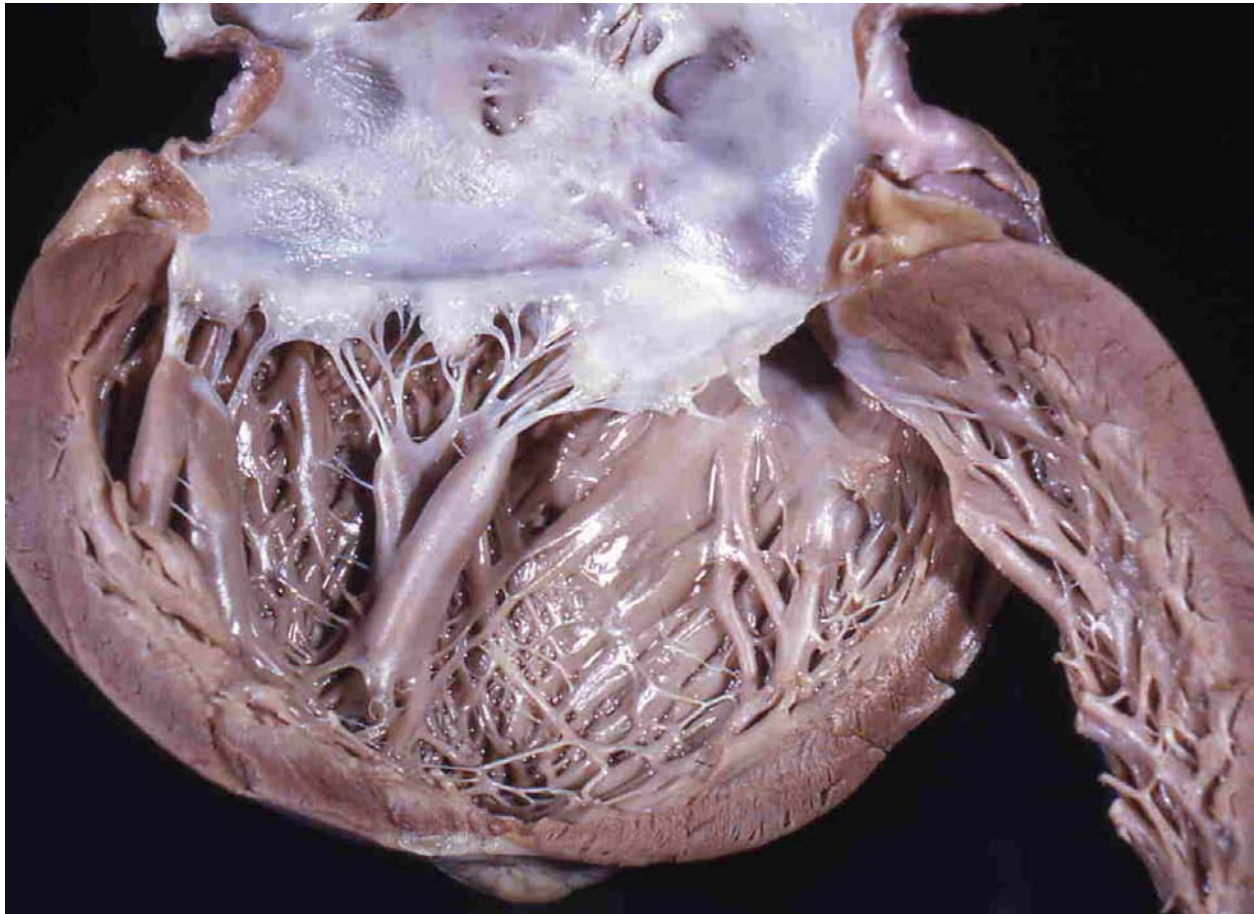
Table 2: Cardiovascular lesions in HHV-6 infection. Cases with positive serology only are merely suggestive and not confirmed by other studies. Abbreviations: nl = normal; PCR = polymerase chain reaction; EMB = endomyocardial biopsy; BMTx = bone marrow transplant

In essence, there exists a striking difference between the frequency of demonstrating HHV-6 infection of vascular endothelial cells (which carry the HHV-6 CD46 receptor) and the rarity of cardiovascular diseases. Some cases of myocarditis showed a coinfection of parvovirus B19 with HHV-6.

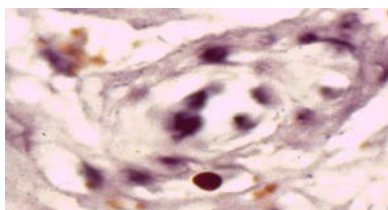
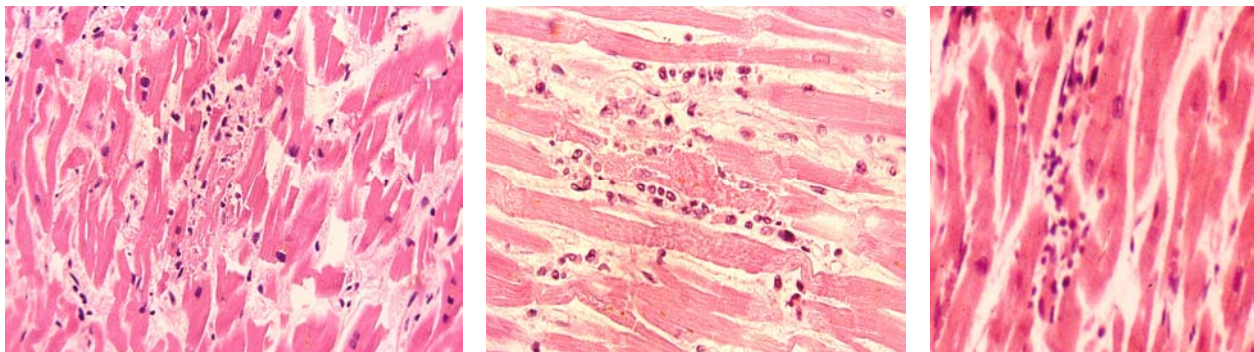
De Ona and colleagues reported that HHV-6 is frequently reactivated in patients with cardiac transplants. Reactivation commonly occurs coincident with active cytomegalovirus (HCMV) infection, and it is the HCMV that usually causes posttransplant disease.

5.2 Figures (see following pages)

5.2 Figures



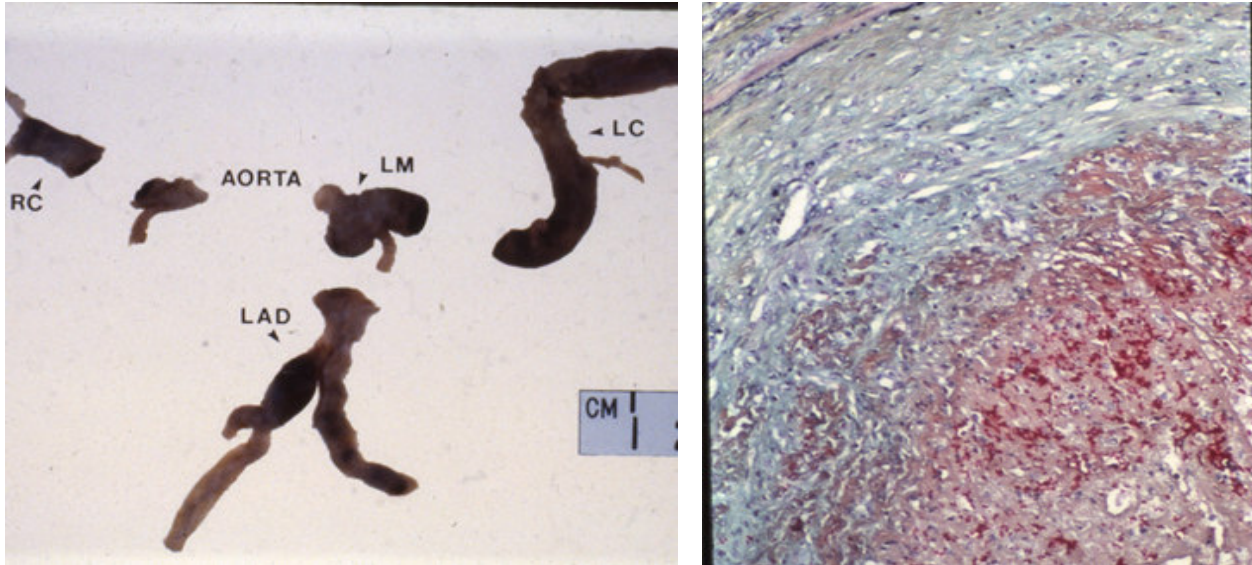
Dilated cardiomyopathy in HHV-6A positive 53 years old AIDS patient



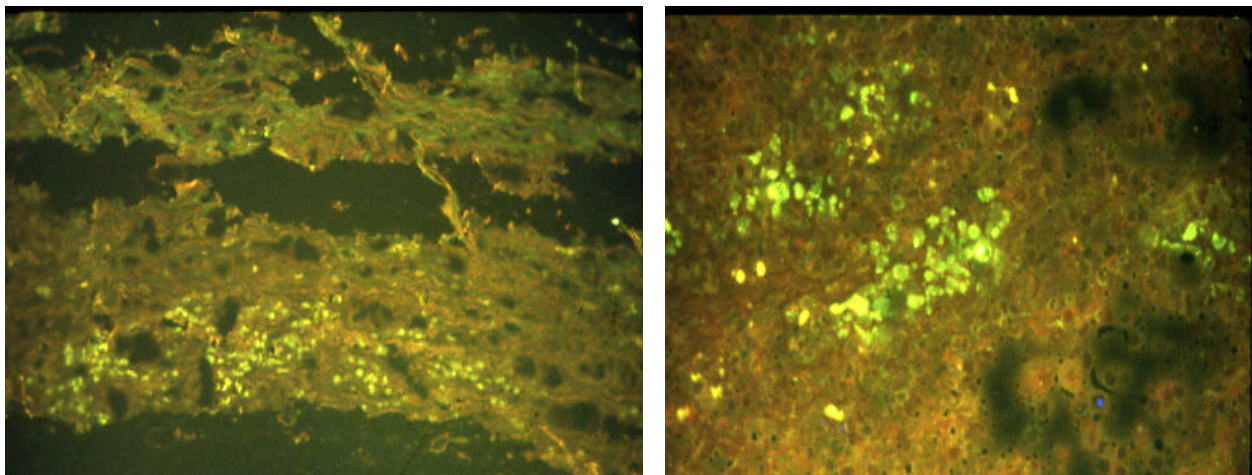
Various cases of myocarditis in HHV-6 positive AIDS patients (top) with occasional demonstration of HHV-6A DNA in vascular endothelial cells by in situ hybridization (left) No other viruses shown.

HHV-6 in Kawasaki's Disease (mucocutaneous lymph node syndrome)

(J. Luka et al., 1995)



Kawasaki's disease: multiple aneurysms of coronary arteries (left) secondary to coronary arteritis (right); identification of branches of coronary arteries: RC right circumflex, LAD left anterior descending, LM left main, LC left circumflex, Aorta indicates the site of the aortic orifice of coronary arteries.

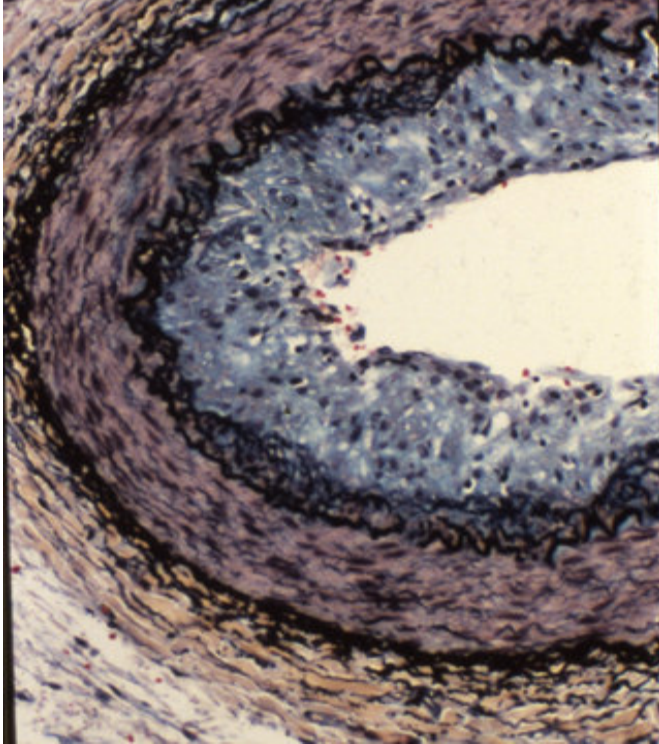


In situ PCR for HHV-6 in inflammatory sites of Kawasaki's coronary arteritis

Luka J, Gubin J, Afflerbach C, Carsopn SD, Krueger GRF: Detection of Human Herpesvirus-6 (HHV-6) genomes by in situ PCR in tissues from Kawasaki's disease and in coronary arteries of transplanted hearts. *Cell Vision* 4: 371-372, 1995

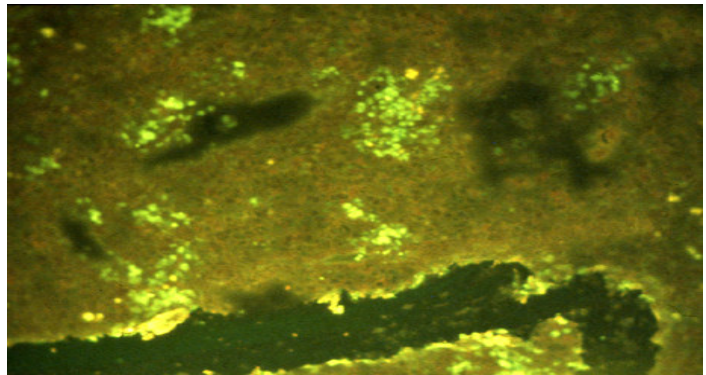
HHV-6 in coronary arteries of transplanted hearts

(Luka et al., 1995; see last page)



Proliferative coronary arteritis in allotransplanted heart

In situ PCR for HHV-6 coronary arteries



5.3 Further Reading

Buja LM. HHV-6 in Cardiovascular Pathology. Chapter 18 in Krueger GRF, Ablashi DV (eds.) Human Herpesvirus-6, 2nd. edition. Elsevier Science Publ, Amsterdam-London 2006

Fukae S, Ashizawa N, Morikawa S, Yano K. A fatal fulminant myocarditis with human herpesvirus-6 infection. Intern Med 39: 632-636, 2000

De Ona M, Melon S, Rodriguez JL, Sanmartin JC, Bernardo MJ. Association between human herpesvirus type 6 and type 7, and cytomegalovirus disease in heart transplant recipients. Transplant Proc 34: 75-76, 2002

6. RESPIRATORY SYSTEM

6.1 Introduction

Salivary glands and the respiratory system appear to constitute primary targets for HHV-6 infection and persistence, yet HHV-6 associated diseases in these tissues are rather rare in immunocompetent persons. A summary of HHV-6 associated disorders in the respiratory system is presented in **Table 3**. A comprehensive review of such diseases was recently prepared by Sebastian Schmidt and colleagues (2006).

Pathologic Entity	Patient	Immune Status	HHV-6 Testing
Rhinopharyngitis	children	nl	serology
katarrheic tracheobronchitis	children	nl	serology
obstructive bronchiolitis	children	nl	serology
interstitial pneumonitis NIP	children, adults	nl, AIDS, post-transplant	serology, IHC, ISH, PCR
interstitial pneumonitis LIP	adults	AIDS	serology, IHC, ISH, PCR
dual infection pneumonitis	adult	immune deficient	serology, IHC, ISH, PCR

Table 3: Rare cases of respiratory diseases caused by HHV-6 infections. The first 3 entities in children may accompany exanthema subitum. Most other cases occur in some kind of immune deficiency including AIDS and transplant recipients. Dual infections in the latter patients consist of reactivated HHV-6 plus pneumocystis carinii, Legionella