7. GASTROINTESTINAL SYSTEM INCLUDING LIVER, BILIARY TRACT, EXOCRINE PANCREAS

7.1 Introduction

As indicated above, salivary glands are a common site of HHV-6 infection and persistence, yet are not frequently affected by HHV-6 induced disease. The HHV-6 load in salivary glands appears increased in Sjogren's syndrome similar to the Epstein-Barr virus. Although clinical GI symptoms are occasionally observed in HHV-6 infections (see Chapter 3), GI diseases aside from few hepatitides are uncommon. We have seen elevations of liver enzymes quite regularly in HHV-6 associated infectious mononucleosis — even more prominent in dual infection by EBV and HHV-6. We have also studied the possible influence of HHV-6 infection on other liver diseases such as those by hepatitis B or C virus

infections and by alcohol abuse. While there appears to be a higher incidence of certain autoantibodies in alcoholoc liver disease and HBV hepatitis with coincident HHV-6, the course of HCV hepatitis seems unchanged. The data of this pilot study, though, need more extensive investigation. Wagner reported of a child with inherited immune deficiency syndrome and HHV-6 infection who suffered from cholangiohepatitis with HHV-6 p41 antigen in bile duct epithelia. The further course was complicated by interstitial pneumonitis and final lethal necrotizing encephalitis with massive HHV-6 antigen and DNA in the brain (see also Chapter 10). **Table 4** summarizes our current state of knowledge of HHV-6 infections and suggestive Gl/liver diseases, which is reviewed in more detail by Yoshikawa (2006).

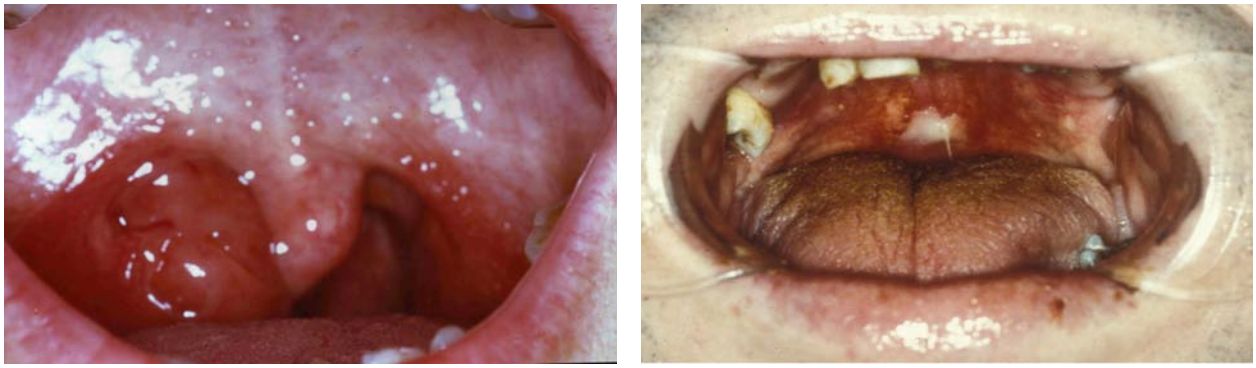
Pathologic Entity	Patient	Immune Status	HHV-6 Testing
Diarrhea	children, adults	nl, post transplant	serology, DNA in stools 1and in intestinal epithelia
intussusception	children	nl	serology, PCR in mesent. LN
hepatitis	children, adults	nl, immune deficient	serology, IHC, ISH, PCR
cholangiohepatitis	child	immune deficient	serology, IHC, ISH

Table 4: Sporadic cases of HHV-6 associated diseases in GI tract and liver. Abbreviations: nl = normal; PCR = polymerase chain reaction; LN = lymph node; IHC = immunohistochemistry; ISH = in situ hybridization.

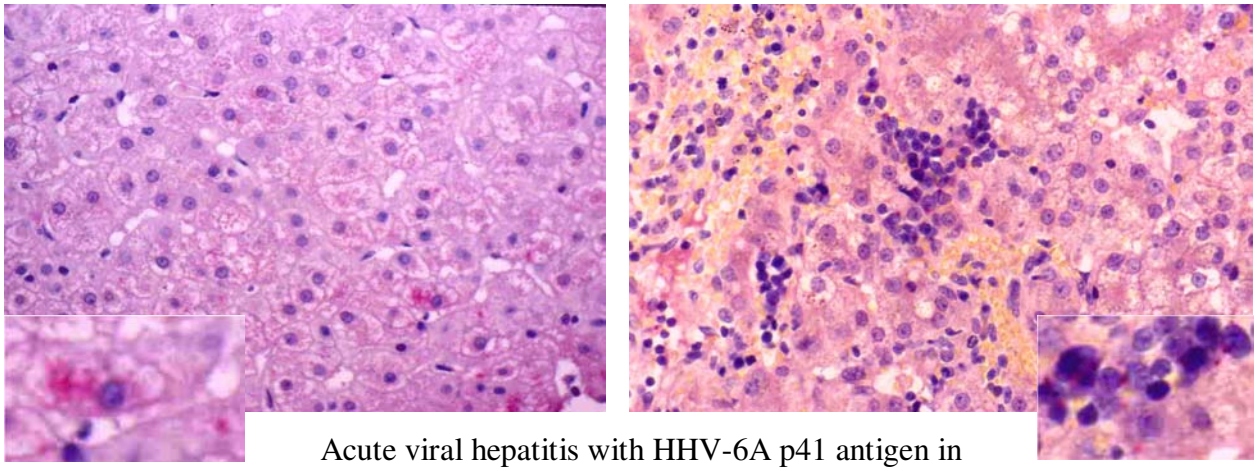
Diarrhea frequently accompanies other diseases such as exanthem subitum. Hepatitides were reported as fulminant, with features of acute yellow (red) atrophy or Reye's syndrome, acute and chronic. HHV-6 DNA was demonstrated in bile duct epithelia (1 case) and in nuclei of hepatocytes or in portal vein endothelial cells. Among other cases with elevation of hepatic enzymes and positive HHV-6 serology are hemophagocytic syndrome, post-transplant states and Gianotti-Crosti syndrome (see chapters of respective organ systems). Patients with liver transplantation show an increased risk of HHV-6 reactivation, frequently associated with HCMV infection. HHV-6 reactivation does not appear to influence acute rejection but may possibly have a certain relation to later (30 days post Tx) rejection. Carol Durno and colleagues have reviewed the possible impact of HHV-6 reactivation in patients with gastrointestinal transplants and conclude that HHV-6 may constitute a risk factor for post-transplant hepatitis and pneumonitis.

7.2 Figures (see next page)

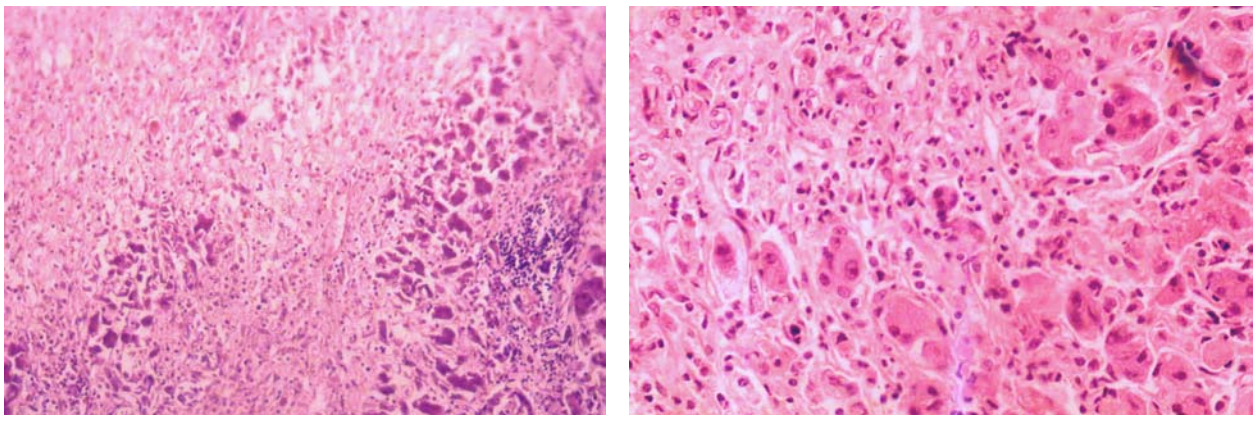
7.2 Figures



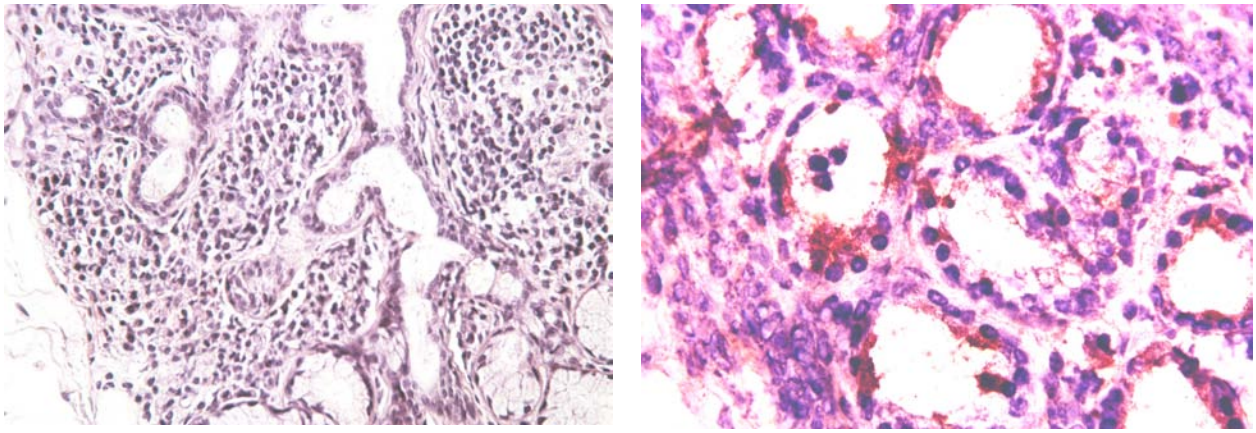
Acute oropharyngitis with tonsillar hypertrophy in a child (left) and chronic oropharyngitis in a 57 year old male without overt immune deficiency (right); the latter was initially thought to suffer from CMV infection.



Acute viral hepatitis with HHV-6A p41 antigen in hepatocytes (left) and in infiltrating lymphoid cells (right)



Lethal necrotizing hepatitis in a child with HHV-6 positive serology & virus isolation



Lip biopsy from patient with Sjoegren's syndrome showing lymphocytic infiltration, glandular atrophy (left) and HHV-6 viral antigen in glandular cells by immunohistochemistry (right); not shown are occasional virus-positive lymphoid cells.

TABLE 22.1.
Inflammatory infiltrate (focus score and % infiltrated area), titers of anti-HHV-6 antibodies in serum and immunohistochemical staining in salivary glands of SS patients (SS) and controls (CTRL) (ND denotes not done)

Nr.	Age	Sex	Diagnosis	Focus score/ % infiltr. area	Serum anti-HHV-6			HHV-6 saliv. gland
					IgG	IgM	IgA	
1	27	F	SS	2.5/2.7	160	0	40	+ + +
2	62	F	SS	4.0/4.6	1280	0	0	+ + +
3	65	F	SS	5.5/20.2	320	0	40	(+)
4	64	F	SS	3.0/10.3	40	0	0	(+)
5	64	F	SS	5.0/46.0	320	0	0	(+)
6	59	F	SS	4.0/N.D.	80	0	0	+ + +
7	43	F	SS	4.0/ < 0.1	640	20	0	+ +
8	53	F	SS	3.5/N.D.	1280	0	0	+ + + +
9	26	F	SS	9.0/4.6	2560	0	0	N.D.
10	44	F	SS	6.0/1.7	160	0	0	N.D.
11	36	F	SS	3.0/10.8	2560	80	40	N.D.
12	50	F	CTRL	0.0/ < 0.1	320	0	0	N.D.
13	68	F	CTRL	0.0/ < 0.1	40	0	40	+ + + +
14	70	F	CTRL	0.0/ < 0.1	80	0	0	+ +
15	76	F	CTRL	0.0/ < 0.1	40	0	0	+ + + +
16	63	F	CTRL	0.0/ < 0.1	320	20	0	+ +
17	54	M	CTRL	0.0/ < 0.1	40	20	0	+ +
18	74	F	CTRL	0.0/N.D.	N.D.	N.D.	N.D.	(+)
19	52	F	CTRL	0.5/ < 0.1	0	0	0	N.D.
20	54	F	CTRL	1.0/ < 0.1	80	0	0	N.D.

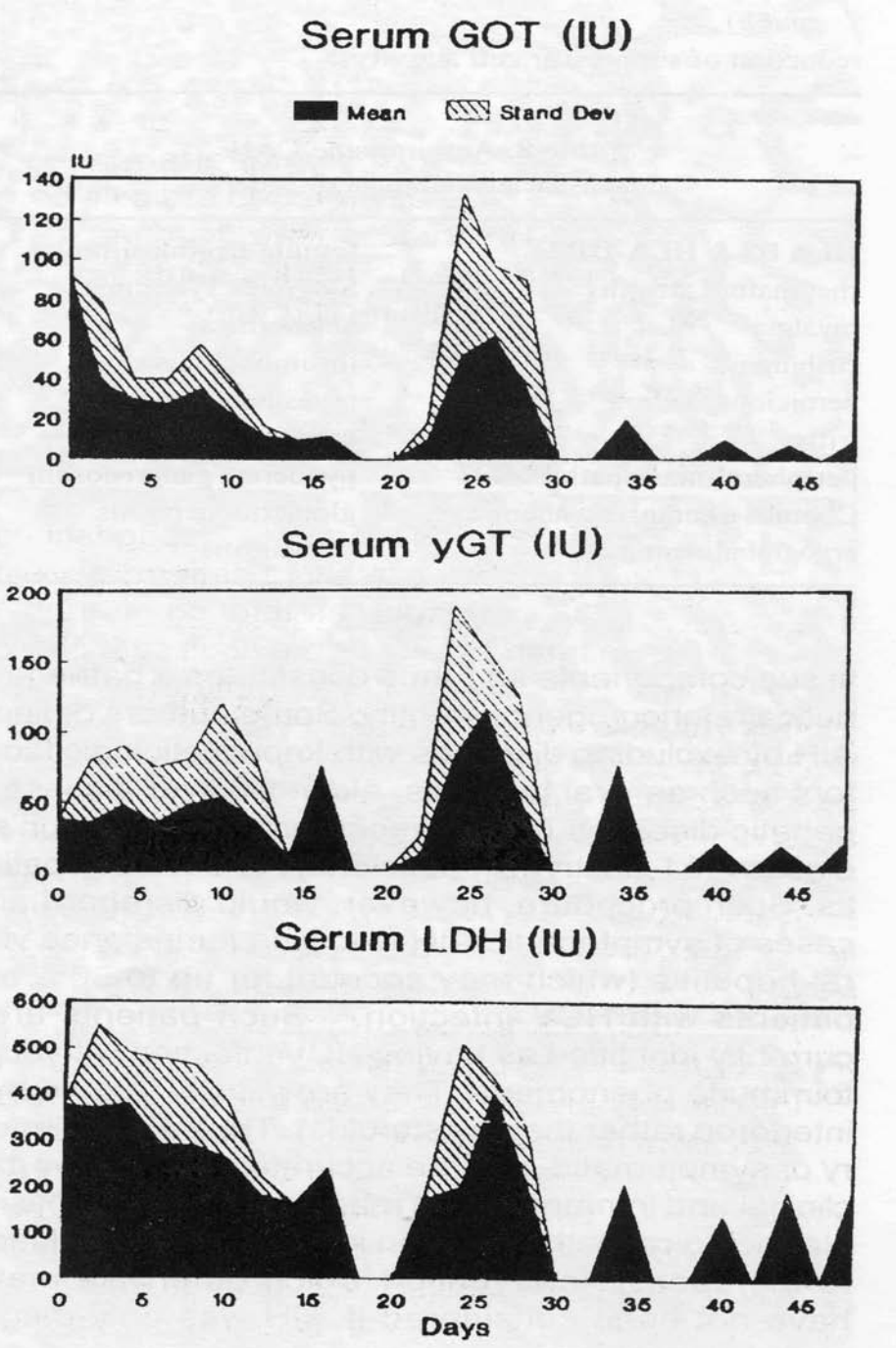


Figure 6. *Liver enzyme patterns in 58 cases of EBV infectious mononucleosis complicated by HHV-6 reactivation: note second peak of elevated enzymes about 4 weeks after onset of the disease.*

7.3 Further Reading

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