Correlation of HBV and HCV with CH, LC, HCC in Liver Biopsied Tissue at Rajavithi Hospital

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Retrospective study in Clinicopathology of 66 surgical liver tissue from adult Thai patients admitted at Rajavithi Hospital, in Bangkok, during December 2002-September 2003 (10 month periods).

The main purposes are: 1) To find the correlation of HBV, HCV with CH, LC, HCC. 2) To compare the correlation of Hepatocyte, AFP, CEA (IHC) in malignant cells, which one is the best usage to confirm the diagnosis of HCC in both primary and metastasis. 3) To review the clinicopathology of all these 66 liver samples.

The results were significant correlation of HBsAg (serology) with HCC ($p = 0.010$), and also significant correlation of HBsAg (IHC in liver tissue) with CH, LC ($p = 0.038, 0.021$ respectively).

Although no significant correlation ($p > 0.05$) of HCV (positive anti HCV) with CH, LC, HCC; the causes due to the small sample sizes and short period study are possibly bias factors.

The authors concluded that Hepatocyte or Hep-Par I is the best immunocellular marker for malignant liver cells both in primary and metastasis ($p < 0.001$). The AFP, CEA show no correlation ($p = 0.999, 0.670$). The authors found other interesting non-viral related liver disease, common, uncommon, tumor and tumor-like (pseudotumor) lesions in the liver from the present study.

The results of significant correlation of HBV (HBsAg) with CH, LC, HCC is one good evidence to further support The National HBV Vaccine Program for the uninfected population, which has been sponsored by the Thai Government, The Ministry of Public Health since 1992 and be one of the best and successful Thai Public-Health Policy.

Keywords: *HBV, HCV, CH, LC, HCC, IHC of HCC, Liver tumor, Tumor-like lesions in liver*

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In the area of the New World times for hepatology, advances have been achieved in hepatic virology[1,2], from A through G and the creation of readily available and reliable tests. The recognition that hepatitis viruses B and C are the major causes of CH (chronic hepatitis), LC (cirrhosis) and are important precursors to the development of HCC (hepatocellular carcinoma) justify the emphasis on correlation with these agents, which were the aims of the present studies[1-5].

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Knowledge regarding liver disease, hepatic viral disease in Thailand[6-12], hepatitis B is a triumph of modern medicine to treat, to manage and prevention. In a generation the hepatitis B virus has been discovered and cloned, along with delineation of the natural histories of the several diseases it causes, creation of an effective vaccine and development of therapies which are effective in some. The ever-widening use of the hepatitis B vaccine is beginning to have the hoped-for impact on the prevalence of hepatitis B in many settings with impressive reductions in the risk to a neonate born to a mother who has hepatitis B and the virtual elimination of transfusion

and occupationally-acquired hepatitis B. The hepatitis B vaccination has been applied in Thailand as one of the Thailand National Health Programs supported by the Ministry of Public Health since 1992[6].

The 1990s were described as the decade of hepatitis C[1,2]. Following the identification of the hepatitis C virus as the 1990s began, a cascade of observations led to the recognition that hepatitis C is the major cause of chronic hepatitis and cirrhosis in the United States, Italy, Japan, etc. and that the progression of the disease is often clinically silent. Hepatitis C has been an overriding interest of many who care for patients with liver disease. The goals for hepatology include the development of a vaccine to prevent hepatitis C[3-5] and more effective therapies for the millions of patients who are already infected. In Thailand VH, CH, LH, HCC has been one of the most concern health problems, chronic disease to total outcome. Studies on etiology, prevention and modern treatment have been intensively studied[6-12].

Objective

The objectives of the present study were

1. Emphasis on finding of HBV (IHC on liver tissue), HCV (positive anti-HCV) in CH, LC and HCC.

2. The most reliable immunohistological markers of IHC to confirm the malignancy to be hepatocyte.

3. Other liver diseases presented with altered LFT, tumor or tumor-like lesion, primary and metastatic tumor in the liver.

Material and Method

Retrospective studies of surgical pathology specimens from 66 patients admitted to Rajavithi Hospital from December 2002-September 2003; all liver tissue sent to the Department of Pathology. Final histopathological diagnosis had been made from review of all cases from these collections, the tissue paraffin blocks were recut, added more histochemical stains, IHC (Avidin- biotin System) (Hepatocyte or Hep-Par I (clone OCH 1E5), AFP (clone ZSA06), CEA, HBsAg, and other related cellular markers). The clinical part, past and present clinical history. Laboratory investigation, imaging findings, management and progresssion had been studied from Medical Records. The available records and existing data are presented in appendix. Microscopic illustrations of representative cases are presented in Fig. 1-43.

Statistical analysis (Table 1-6) was performed by using SPSS for Windows Version 11.0. Results

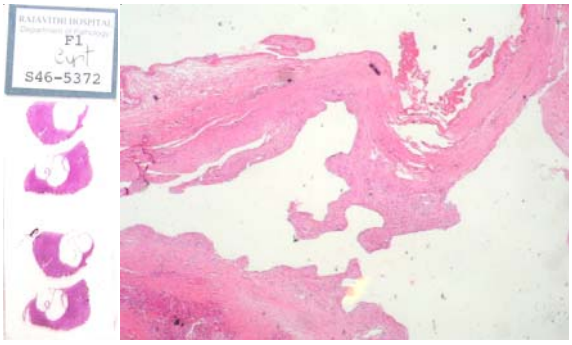

Fig. 1, 2 PCD. A liver cyst is lined by single thin layer epithelium. Excisional biopsy, H&E, x10 (left)/ x40 (right) (S46-989)

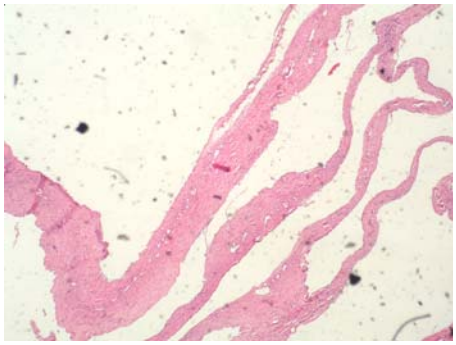

Fig. 3 PCD. Multiple cysts, lined by single thin or cuboidal epithelium. H&E, x40 (S46-5241)

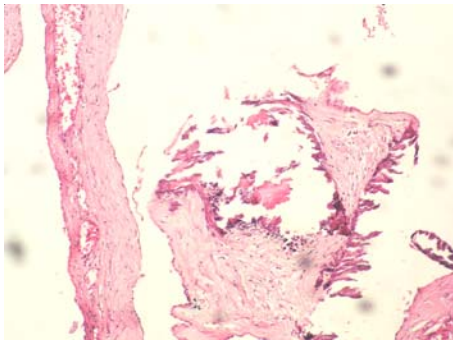

Fig. 4 PCD. Multiple cysts with focal calcified cyst walls. H&E, x100 (S46-5241)

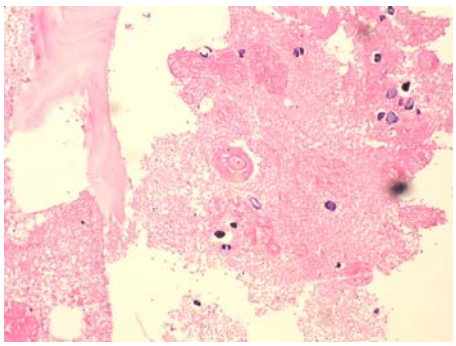

Fig. 5 Echinococcal cyst contents. Mother cyst wall, capsule, calcified areas, H&E, x100 (S46-6805)

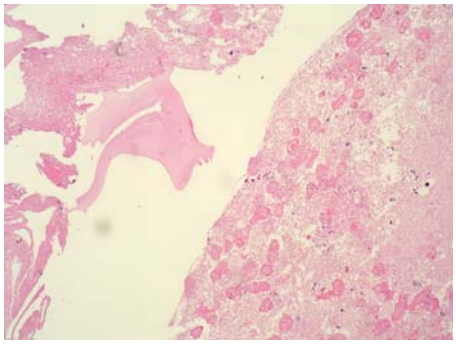

Fig. 6 The cyst wall, with the germinal layer and adjacent avascular, refractile, chitinous laminated membrane. H&E, x40 (S46-6805)

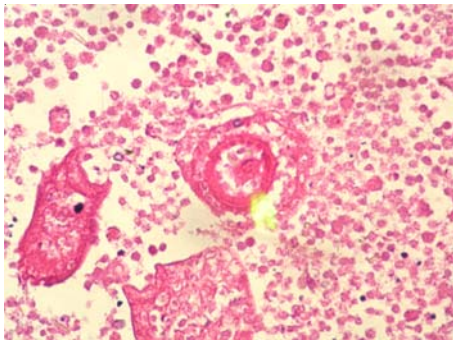

Fig. 7 Daughter cysts, Multiple protoscolices of Echinococcus granulosus within daughter cyst. H&E, x400 (S46-6805)

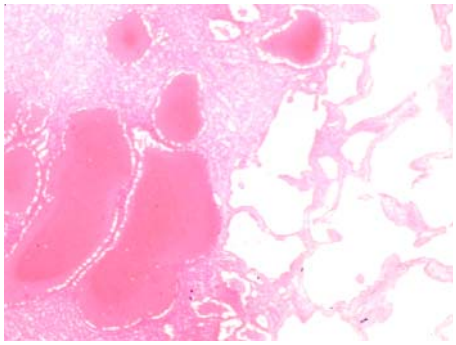

Fig. 8 Cavernous hemangioma, composed of vascular channels lined by a single layer of endothelium set in liver H&E, x40 (S46-424)

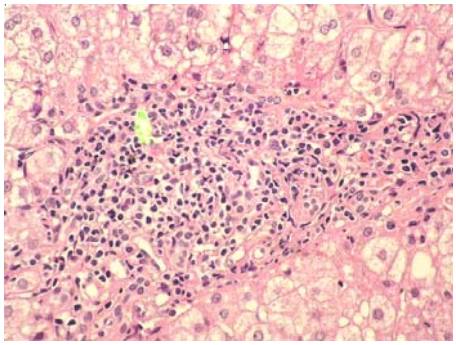

Fig. 9 CH (HCV), grade 3 (activity). Portal triad. Liver cells are swollen and rounded in the zone of piecemeal necrosis.H&E, x400 (S46-3475)

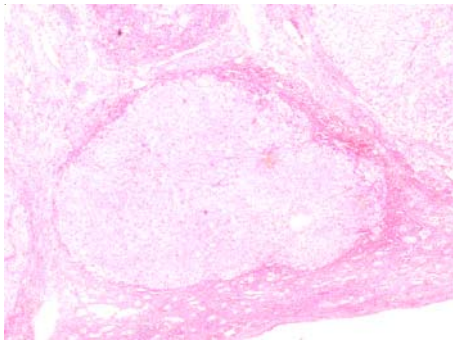

Fig. 10 CH and LC (HCV). One cirrhotic nodule, surrounded by inflamed portal triads with fibrosis. H&E, x40 (S46-5747)

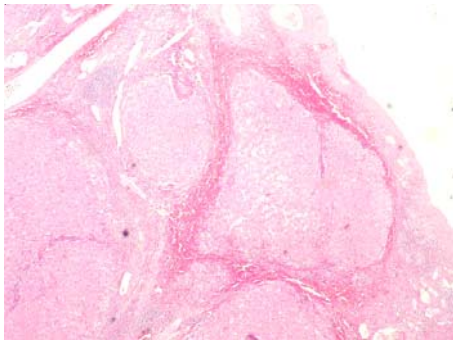

Fig. 11 CH&LC (HBV). Several cirrhotic nodules varying in sizes, surrounded by inflamed triads. H&E, x40 (S46-5747)

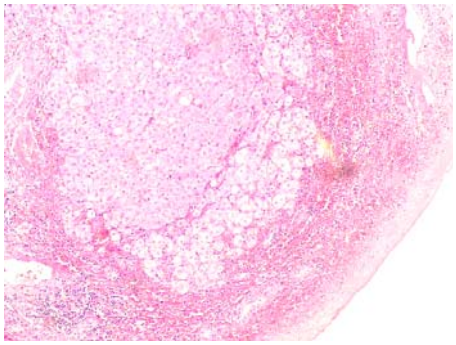

Fig. 12 CH&LC (HBV), Dysplasia and neoangiogenesis at the rim of cirrhotic nodules. H&E, x100 (S46-5747)

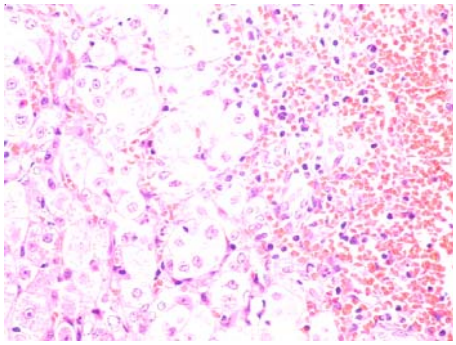

Fig. 13 Note the LLC with dysplastic, high N/C ratio and several new blood vessels (right). H&E x400 (S46-5747)

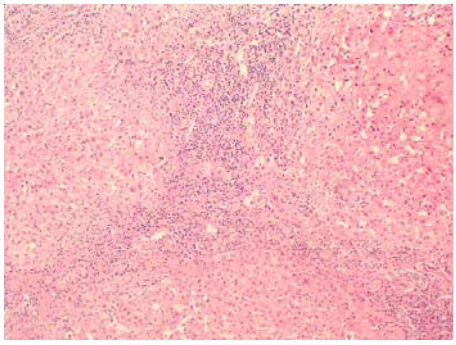

Fig. 14 CH&LC (HBV). H&E x100

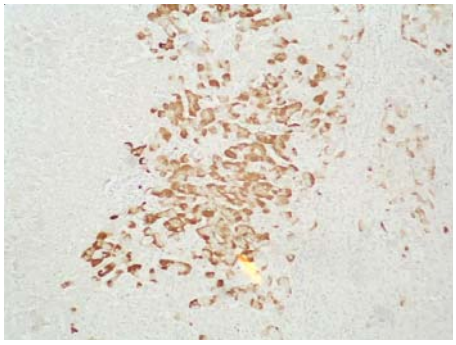

Fig. 15 CH (HBV). IHC (HBsAg+) , x100 (S46-1933)

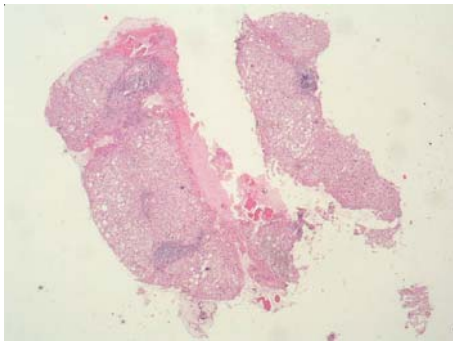

Fig. 16 CH, LC, Positive anti HCV note grade 2 or CH (activity), cirrhosis H&E x40 (S46-3475)

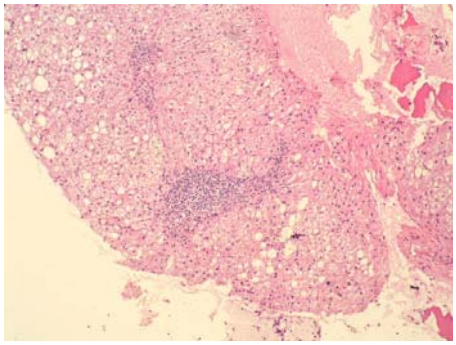

Fig. 17 Dense inflammatory infiltrates in portal triads. H&E x100 (S46-3475)

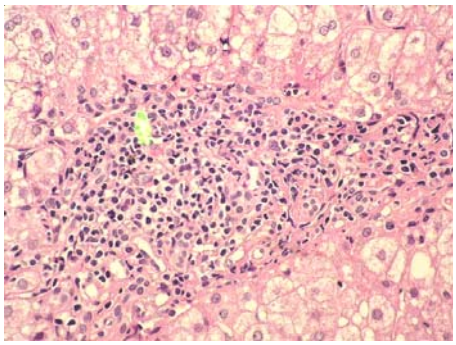

Fig. 18 Higher magnification of portal triads, dense lymphoid aggregation, piecemeal necrosis, fatty changes H&E x400 (S46-3475)

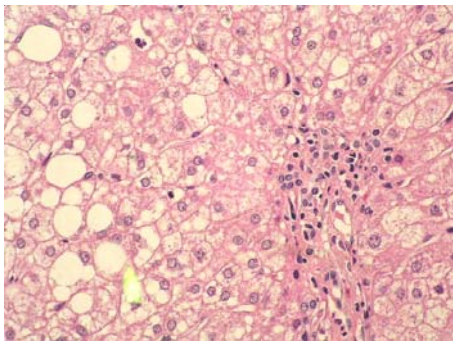

Fig. 19 Note micro and macro vesicular fatty changes in hepatocytes, fatty changes and lymphoid aggregations are common findings in CH caused by HCV (Fig. 18) H&E x400 (S46-3475)

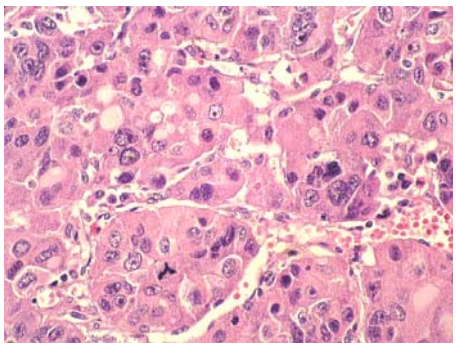

Fig. 20 HCC, compact type, anaplastic hepatocytes with atypical mitoses H&E x400 (S46-3444)

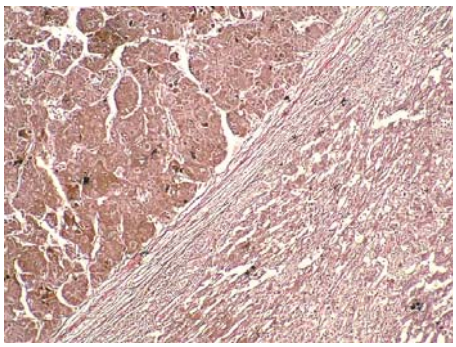

Fig. 21 Tumor nodule compress the adjacent liver parenchyma. IHC (Hep-Par I) x100 (S46-3444)

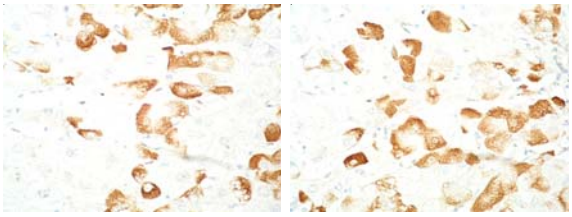

Fig. 22, 23 IHC HBsAg positive, note the brownish granules in cell membrane and cytoplasm.IHC (HBsAg) x400

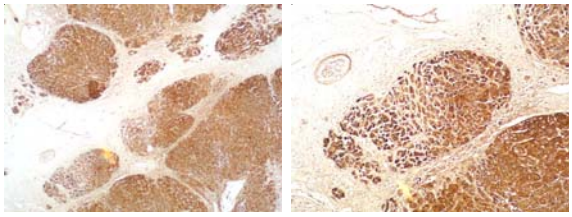

Fig. 24, 25 LC , Hepatocyte (Hep-Par 1) positive in liver cell .IHC (Hep-par1) x40 (S46-1933)

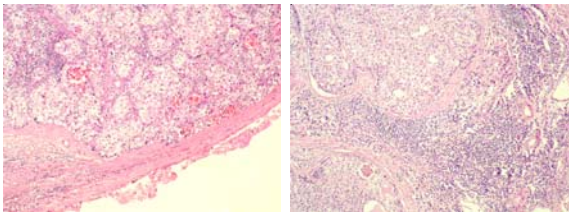

Fig. 26 HCC, compact type; note the cirrhotic nodules, chronic inflammatory infiltrates at portal triads. H&E x100 (S45-10692)

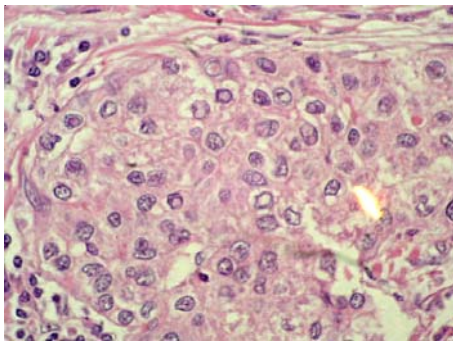

Fig. 27 HCC, compact type H&E x600 (S45-106692)

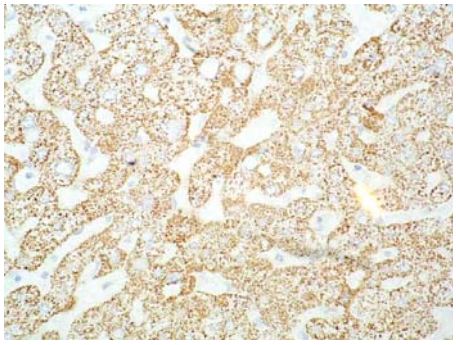

Fig. 28 HCC, trabecular type, Positive Hepatocyte or Hep-Par 1. IHC (Hep-Par 1) x100 (S45-10692)

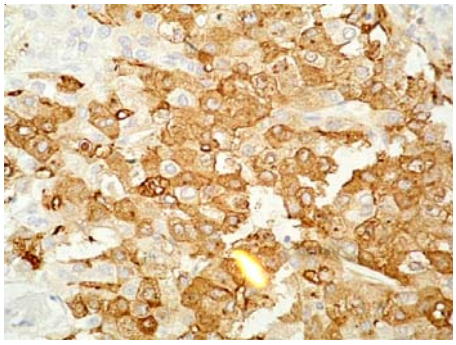

Fig. 29 HCC, trabecular type Positive AFP, IHC(AFP) x400

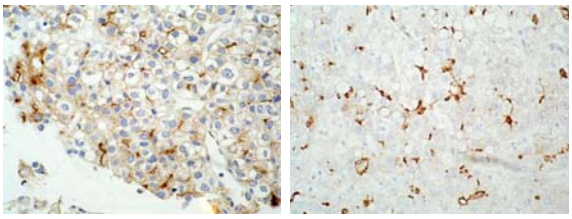

Fig. 30 HCC, Positive CEA at bile caniliculi (Canilicular pattern of CEA in HCC), IHC (CEA) x400 (S4-5747, Lt., S46-6458, Rt.)

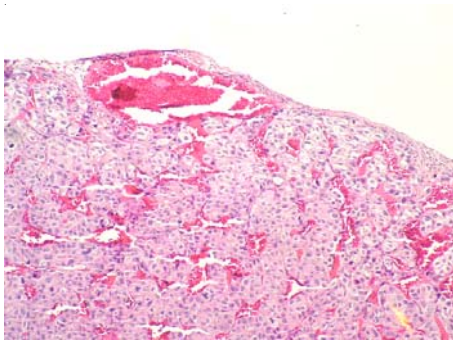

Fig. 31 HCC, ruptured at the rim and capsule, trabecular type. H&E x100 (S46-7528)

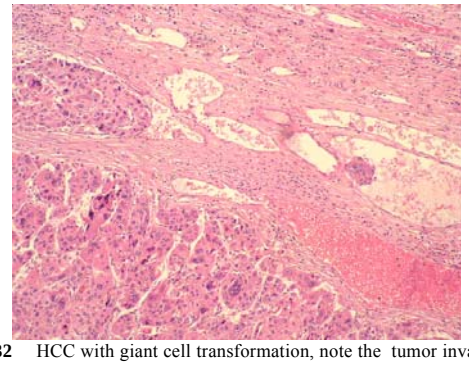

Fig. 32 HCC with giant cell transformation, note the tumor invades in vascular space, surrounded by neoangiogenesis. H&E x100 (S46-3642)

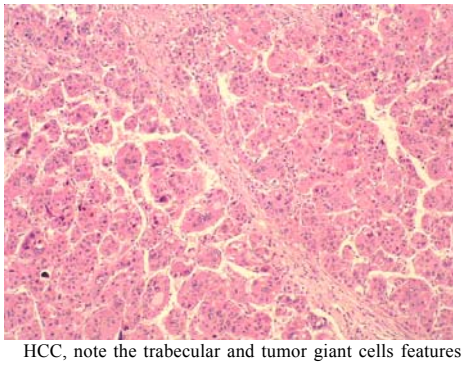

Fig. 33 HCC, note the trabecular and tumor giant cells features H&E x100 (S46-3642)

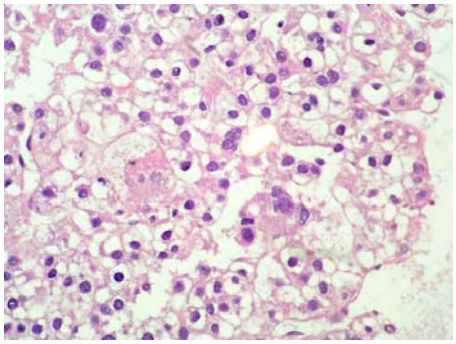

Fig. 34 HCC, clear cell type H&E x400 (S46-6991)

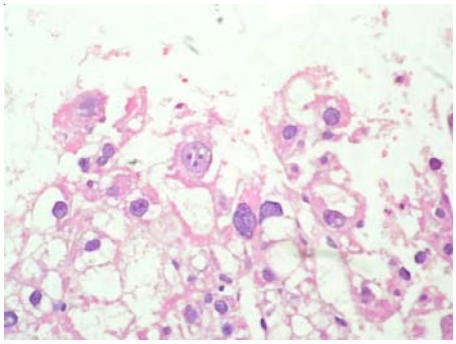

Fig. 35 HCC, clear cell type, note the clear cytoplasm H&E x600 (S46-6991)

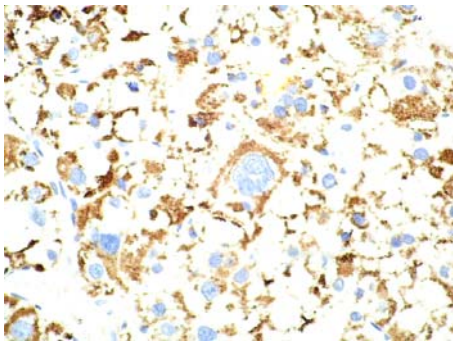

Fig. 36 HCC, clear cell typePositive Hepatocyte, exclusion of Metastatic renal cell carcinoma (clear cell type), metas neuroendocrine, tumor and other tumor with clear cell changesIHC (Hepar1) x400 (S46-6991)

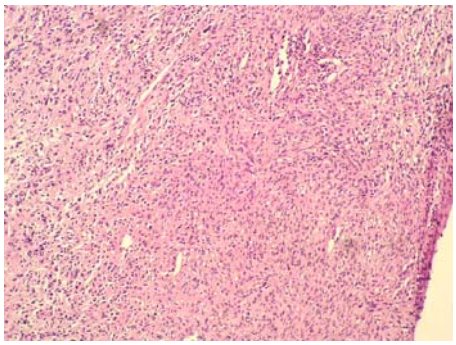

Fig. 37 Metastatic spindle cell sarcoma to liver (GIST, primary in stomach wall) H&E x100 (S46-3293)

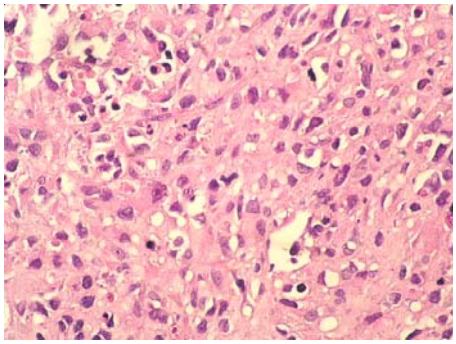

Fig. 38 Malignant spindle cells and epithelioid cells with atypical mitoses, metastasis from stomach H&E x400 (S46-3293)

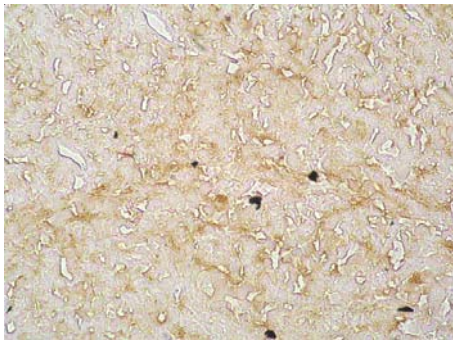

Fig. 39 Metastatic to liver, Gastrointestinal Stromal Tomor, primary in Gastric wall.IHC (CD117, cKit) positive X100 (S46-3293) Negative SMA (not shown)

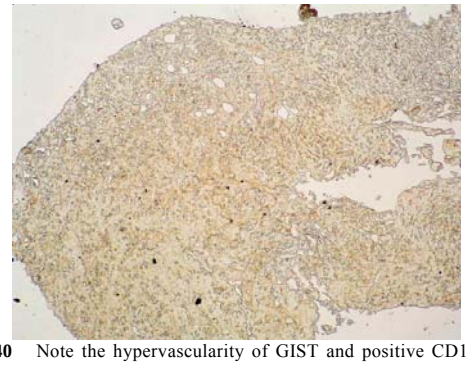

Fig. 40 Note the hypervascularity of GIST and positive CD117IHC (CD117, cKit) positive, x40 (S46-3293)

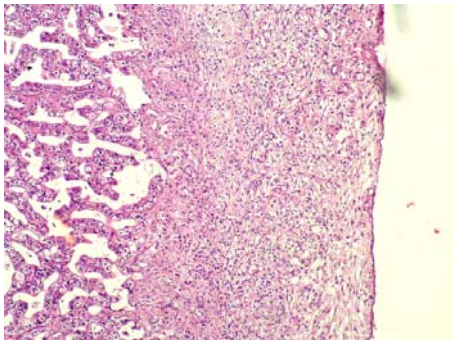

Fig. 41 CC (Bile duct carcinoma) Adenocarcinoma involving liver tissue, infiltrating the capsule(Rt.), forming glands, bands of cells (Lt.) H&E x100 (S46-5834)

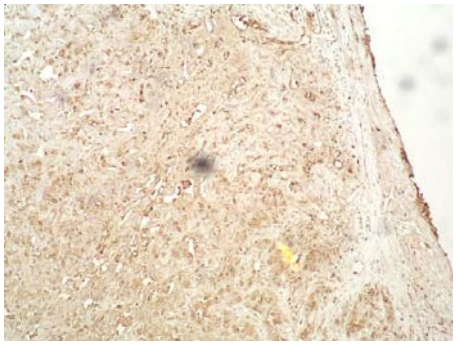

Fig. 42 CC, expression of CEA, no canalicular pattern of positive CEA in HCC, compare to Fig. 30IHC (CEA) x100 (S46-5834)

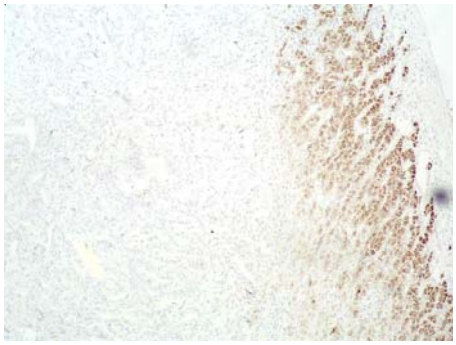

Fig. 43 CC, the malignant glands show negative Hep-Par 1(Lt.) ; the adjacent normal liver tissue express Hepatocyte-antigen (Rt.) IHC (Hep-Par1) x100 (S46-5834)

Table 1. Demographic data

Sex	N (%)	Median age (min-max)
Male	35 (53.0)	44 (12-79)
Female	31 (47.0)	51 (19-89)
Total	66 (100.0)	47 (12-89)

Table 2. Biochemistry data (Liver Function Test)*

Biochemistry	Median (min-max)
Total protein	7.3 (3.2-8.3)
Albumin	3.3 (1.4-4.4)
Globulin	3.8 (1.8-5.7)
Total bilirubin	1.0 (0.2-25.5)
Direct bilirubin	0.5 (0.04-19.6)
AST	66.5 (5-3610)
ALT	54.0 (11-1248)
ALP	191.0 (36-883)

* Unit in the table in according to International Unit

Table 3. Serologic tumor markers data

Tumor marker	Median (min-max)
AFP	5.55 (0.4-6690)
CEA	2.90 (1.1-747)
CA 125	30.80 (6.3-393.2)
CA 19-9	31.75 (0.8-20000)

Table 4. Variables & Chronic hepatitis

Variables	Chronic hepatitis		
	Positive (%)	Negative (%)	p-value
Anti HCV (ELISA)			
Positive	5 (45.4)	1 (16.6)	0.330
Negative	6 (54.6)	5 (83.4)	
HBsAg (ELISA)			
Positive	6 (46.2)	3 (23.1)	0.411
Negative	7 (53.8)	10 (76.9)	
Anti HBsAg(ELISA)			
Positive	3 (60.0)	4 (50.0)	0.999
Negative	2 (40.0)	4 (50.0)	
HBsAg (IHC)			
Positive	11 (68.7)	3 (23.1)	0.038
Negative	5 (31.3)	10 (76.9)	
Hepatocyte (IHC)			
Positive	7 (70.0)	6 (42.8)	0.240
Negative	3 (30.0)	8 (57.2)	
AFP (IHC)			
Positive	6 (50.0)	4 (44.4)	0.999
Negative	6 (50.0)	5 (55.6)	

Table 5. Variables & Cirrhosis

Variables	Cirrhosis		
	Positive (%)	Negative (%)	p-value
Anti HCV (ELISA)			
Positive	3 (75.0)	3 (23.1)	0.099
Negative	1 (25.0)	10 (76.9)	
HBsAg (ELISA)			
Positive	8 (80.0)	5 (25)	0.138
Negative	2 (20.0)	15 (75)	
Anti HBsAg(ELISA)			
Positive	2 (100.0)	5 (45.5)	0.462
Negative	0 (0.0)	6 (54.5)	
HBsAg (IHC)			
Positive	8 (80.0)	6 (31.6)	0.021
Negative	2 (20.0)	13 (68.4)	
Hepatocyte (IHC)			
Positive	6 (75.0)	7 (43.8)	0.211
Negative	2 (25.0)	9 (56.2)	
AFP (IHC)			
Positive	5 (55.5)	5 (41.6)	0.670
Negative	4 (44.5)	7 (58.4)	

Table 6. Variables & Hepatocellular carcinoma

Variables	Hepatocellular carcinoma		
	Positive (%)	Negative (%)	p-value
Anti HCV (ELISA)			
Positive	2 (40)	4 (33.3)	0.999
Negative	3 (60)	8 (66.7)	
HBsAg(ELISA)			
Positive	5 (83.3)	4 (20.0)	0.010
Negative	1 (16.7)	16 (80.0)	
Anti HBsAg (ELISA)			
Positive	2 (100.0)	5 (45.5)	0.462
Negative	0 (0.0)	6 (54.5)	
HBsAg (IHC)			
Positive	8 (61.5)	6 (37.5)	0.360
Negative	5 (38.5)	10 (62.5)	
Hepatocyte (IHC)			
Positive	12 (92.3)	1 (9.1)	<0.001
Negative	1 (7.7)	10 (90.9)	
AFP (IHC)			
Positive	7 (63.6)	3 (30.0)	0.198
Negative	4 (36.4)	7 (70.0)	

were presented as Median (min-max). Chi-Square tests or Fisher's exact tests were used to evaluate significant differences in proportion among variables. The statistical significant difference was considered at the p-value that was less than 0.05. Table 7-14, appendix reveal the basic details in studied processes.

Results

From Dec 2002 to Sep 2003, there were 66 patients with records at Rajavithi Hospital that sent liver tissue to Department of Pathology. The sex and age (M = 34, F = 31; M:F = 1.09) (Table 1), range and average age 49 years (min = 12, max = 89). Liver function test data and serologic tumor markers data are shown in Table 2 and Table 3.

There are 6, 2, 14 cases of final diagnosis of CH, LC, HCC, respectively. From 66 specimens, finding of positive HBsAg (ELISA)/positive HBsAg (IHC)/ positive anti HCV (ELISA) are 6/11/2; 4/8/3; 5/8/2 for CH, LC, HCC, respectively.

Applying Chi-square or Fisher's exact test of statistical analysis. The results are shown in Table 4-6.

From Table 4-6 found that HBsAg (IHC) related to CH and LC show statistically significant (p = 0.038, 0.021, respectively). HBsAg (ELISA) and Hepatocyte (IHC) related to HCC also show statistically significant (p = 0.010, < 0.001, respectively).

Discussion

In the current study, 35 male, 31 female patients with an average age of 49 years (range 12-82), 43 cases of tumor (primary or metastasis to liver)

Table 7. Pathologic TNM staging of primary hepatic epithelial malignancies[44]

T: Primary tumor
- T1: Solitary mass, without vascular invasion
- T2: Solitary mass with vascular invasion, or multiple tumors, non > 5 cm
- T3: Multiple masses > 5 CM or tumor involving a major branch of the portal or hepatic vein(s)
- T4: Tumor with direct invasion of adjacent organs, other than the gallbladder or with perforation of the visceral peritoneum

N: Regional lymph nodes
- N0: Negative regional lymph nodes
- N1: Positive regional lymph nodes

M: Distant metastases
- MX: Cannot be assessed
- M0: No distant metastases
- M1: Distant metastases present

Stage groupings
- Stage I: T1 N0 M0
- Stage II: T2 N0 M0
- Stage IIIA: T3 N0 M0
- Stage IIIB: T4 N0 M0
- Stage IIIC: Any T N1 M0
- Stage IV: Any T any N M1

Adapted from American Joint Committee on cancer. Liver (including intrahepatic bile ducts). In: Cancer staging manual, 6th ed. New York: Springer-Verlag, 2002: 131-6.

Table 8. Histologic grading of hepatocellular carcinoma[32]

Well differentiated (grades I/II of Edmondson and Steinet).

Thin plates, three or fewer hepatocytes thick, that are typically smaller than normal, demonstrate minimal nuclear atypia, and have a nuclear density greater than twice that of the nonneoplastic liver. Fatty change and pseudoglandular architecture are common. Clear-cut histologic distinction from hepatocellular adenoma may not be possible in some cases without finding other, more poorly differentiated foci and knowing the status of the nonneoplastic liver. This pattern is typical of small (< 2 cm) hepatocellular carcinoma.

Moderately differentiated (grades II/III Edmondson and Steiner).

This is typically characterized by a trabecular pattern in which tumor cells are arranged in plates more than three cells thick. Tumor cells are large and have more abudent eosinophilic cytoplasm and distinct nucleoli, compared with well-differentiated tumors. Pseudoglandular structures and bile are usually seen, and tumor giant cells may be present this is the most common type of differentiation seen in advanced (>2 cm) hepatocellular carcinoma.

Poorly differentiated (grades III/IV of Edmonson and Steiner).

Tumor cells have larger and more hyperchromatic nuclei and are typically arranged in a compact (solid) growth pattern with rare or no trabeculae or bile. Pleomorphism may be prominent, and spindle cell or small cell areas may be seen. It may be difficult to recognize as hepatocellular in origin.

Table 9. Hepatocellular carcinoma: cytoplasmic deposits and inclusions[4,5,44]

Deposit or Inclusion	Sensitivity (%)	Comments
Diagnostically useful		
Absence of cytoplasmic mucin	100	May be present in combined HCC-CC, CC or metastatic adeno carcinoma
Bile	5-33	Virtually pathognomonic of HCC
Copper/copper-binding protein	7-41	To date, negative in HCC and metastatic adenocarcinoma
Mallorys hyalin	2-25	In malignant neoplasm, virtually pathognomonic of HCC
Hyaline globules	10-15	Highly suggestive of HCC in malignant hepatic tumor, but metastatic adenocarcinoma and neuroendocrine carcinoma may demonstrate these deposits
PAS-positive DR	-	AFP, A_1AT, A_1ACT, giant lysosomes, other glycoproteins
PAS-negative	-	Megamitochondria, apoptotic bodies, albumin, fibrinogen, other proteins
Ground glass/pale bodies	5-10	Fibrinogen, other serum proteins; HbsAg (usually represents trapped nonneoplastic cells)
Of interest, but not diagnostically useful		
Fat, glycogen (clear cells)	20-40	Predominant in 5-16% of cases
Hemosiderin	Rare, trace amounts	True even in HCC arising in hereditary hemochromatosis
Lipofuscin-like pigment	Rare	When prominent, liver may be black (Dubin-Johnson-like)

and 7 cases of tumor like lesions in the liver, 13 cases of HCC, 1 case of carvernous hemangioma and 1 case of allograft liver. The secondary or metastatic tumor primary were Klatskin's tumor, stomach, colo-rectum, lung, and ovary. 7 cases of liver cysts (3 PCD, 1 simple cyst, 2 pyogenic abscesses, 1 ecchinococcus). 8 cases of only CH, 1 case of secondary hemochromatosis, LC was found in combination with CH, HCC, others; finding of HBV, HCV are shown in appendix, final clinical diagnosis shown in appendix. The authors classified and diagnosed CH, LC using Scheuer system[2] (and the Ludwig and Batts system[13], which is nearly identical) simple, relatively reproducible and generally accepted by hepatologists,summarized as follolws:

Grade 0: No or minimal inflammation

Grade 1: Portal inflammation or lobular inflammation with no necrosis

Grade 2: Mild piecemeal necrosis or focal hepatocellular necrosis

Grade 3: Moderate piecemeal necrosis or severe focal cell damage

Grade 4: Severe piecemeal necrosis with bridging necrosis

The overall grade is based on the most severe degree of portal or lobular injury.

The staging system is as follows:

Stage 0: No fibrosis

Stage 1: Enlarged fibrotic portal tracts

Stage 2: Periportal or portal to portal septa

Stage 3: Bridging fibrosis with architectural distortion, no obvious cirrhosis

Current recommendations are to diagnose CH by etiology, with the biopsy providing an assessment of degree or necroinfactivity (the grade) and fibrosis (The stage) (14-16). The terms chronic persis-

Table 10. Hepatocellular carcinoma: immunohistochemistry[44]

Features	Sensitivity (%)	Comments
Greatest diagnostic utility		
p-CEA (canalicular staining)	50-90	Near 100% specificity; beware trapped nonneoplastic hepatocytes and mimics of canalicular pattern in non HCC; often negative in PD-HCC
AFP	15-70	90-95% specificity; lack of sensitivity; may be positive in PD-HCC
m-CEA (noncanalicular staining)	0-10	Rarely positive in HCC; 60-75% CC or metas. adeno CA positive
HepPar-1	80	90% specificity; beware trapped nonneoplastic hepatocytes; rarely CC or metas. adeno CA positive
ERY-1	90	~95% specificity (few data); may be found in renal cell carcinoma, yolk sac tumor, TCC; staining often focal; normal hepatocytes positive
Some diagnostic utility		
Hepatocyte CK (8,18) versus other CKs	94-100 versus 30-60	Lack of specificity, but of use if only "hepatocyte CK" positive
CD34 (endothelium)	50-100	Rare positive in cirrhotic liver; HCA, FNH; prominent in advanced HCC; 50% of small WD-HCC are negative
Least diagnostic utility and/or few data		
α_1-microglobulin	95	Near 90% specificity; need more data
Albumin	nearly 100	Frequent false-positive results, prominent background staining
Inhibin	5-90	Higher rate appears to be false-positive, biotin not blocked
PTHrP	0	All CC positive; metas. adeno CA may be positive (best frozen tissue)
A_1AT	55-93	Lack of specific and/or sensitivity
EMA	40	Lack of specific and/or sensitivity
B72.3	5-10	Lack of specific and/or sensitivity
Ber-EP4	35	Lack of specific and/or sensitivity
HMFG-2	20	Lack of specific and/or sensitivity
Cu-18	10	Lack of specific and/or sensitivity
TPA	30 (week)	Lack of specific and/or sensitivity
Leu-M1/CD15	5-30	Lack of specific and/or sensitivity
Ferritin	45-70	Lack of specific and/or sensitivity
Factor Xllla	65-70	Lack of specific and/or sensitivity
Synaptophysin	5-10	Focal positivity does not exclude HCC (versus NE tumor)
Chromogranin	5	Focal positivity does not exclude HCC (versus NE tumor)

Table 11. Immunohistochemistry of HCC[5]

Antigen	Result
Hepatocyte (DAKO)	Positive (most useful in diagnosis)
Polyclonal carcino embryonic antigen	Positive (canalicular pattern)
Alpha fetoprotein	Positive or negative
Fibrinogen	Positive or negative
Cytokeratins 8 and 18	Usually positive
Cytokeratins 7 and 19	Usually negative
Cytokeratin 20	Usually negative
Epithelial membrane antigen	Negative
BER EP4	Negative

tent (CPH) and chronic active hepatitis (CAH) are no longer used.

Several systems have been suggested for grading (2,13,16-17) but in daily practice and accepted are the preferred Scheuer system[1-4].

The histologic of chronic hepatitis B is the expression of hepatitis B surface (HBsAg) or core antigen (HBcAg) in hepatocytes[18]. The HBsAg is usually expressed in the cytoplasm and correlated with the presence of "ground glass" hepatocytes. The authors didn't apply HBcAg study which the expression of which is indicative of infectivity[19].

Chronic hepatitis C infection is characterized by a patchy portal infiltrate with dense aggregates of small lymphocytes devoid of plasma cells or eosinophils. These aggregates often surround damaged bile ducts, but duct are not destroyed. The area around the aggregates is often devoid of inflammation or contains a few scattered lymphocytes and occasional plasma cells or eosinophils. Extensive piecemeal necrosis is uncommon but always exist in HBV. These aggregates are characteristic enough to allow a presumptive diagnosis of HCV in the appropriate clinical setting. However, only less than half the cases of chronic hepatitis C have the lymphoid aggregates, with the other cases showing variable degrees of nonspecific portal infiltrate. Although fatty change has

Table 12. Tumors other than usual adeno carcinomas that can be misdiagnosed as hepatocellular carcinoma: confusing pathologic features and helpful diagnostic clues[44]

Tumor type	Confusing pathologic features	Clues to correct diagnosis	
		Routine histology	Immunohistochemistry
Neuroendocrine	Similar cytoarchitectural patterns and CK pattern, hyaline globules; HCC can demonstrate focal + Cg, Syn	Stippled chromatin, nucleoli usually not prominent, sclerosis, peritumoral capillary network	Diffuse, strong + Syn, Cg; -p-CEA (canalicular); HepPar-1, AFP, etc.
Clear cell carcinoma	Similar cytoarchitectural patterns and CK pattern as clear cell HCC	Prominent vascular pattern may be present	-p-CEA, HepPar-1, AFP, etc.
Renal cell carcinoma (non-clear cell)	Similar cytoarchitectural patterns and CK profile as HCC	Prominent vascular pattern may be present	-p-CEA, HepPar-1, AFP, etc.
Squamouse cell carcinoma	Solid sheets and trabeculae, eosinophilic cytoplasm	Intercellular bridges, keratin, sclerosis	-p-CEA, HepPar-1, AFP, etc.
Melanoma	Epithelioid cells and replacing growth pattern can simulate trabecular pattern; prominent nucleoli; intranuclear inclusions common; + S100 and HMB45 have been reported in HCC	No well-formed epithelial features, spindle cells, melanin pigment	Diffuse, strong + HMB45; -CK, -p-CEA, HepPar-1, AFP, etc.
Angiomyolipoma	Epithelioid cells, eosinophilic or clear cytoplasm; may have trabecular pattern with liffle reticulin; HMB45 has been reported in HCC	Spindle cells; fat tortuous, thick-walled blood vessels	Diffuse, strong + HMB45; in epithelioid cells; ± MSA; and SMA; -CK, -p-CEA, HepPar-1, AFP, etc.
Prostate adenocarcinoma	Can have sheetlike growth pattern, large cells, with abundant cytoplasm, round nuclei with prominent nucleoli	Cytoplasm more basophilic; glands usually noted with careful searching; cytoplasmic mucin may be present	+PSA, PSAP; -p-CEA, AFP, HepPar-1, etc.
Angiosarcoma	Thickened cards of hepatocytes; +CD34, other endothelial cells lining cords; CK can be positive in these cells; CD34, etc. also + in endothelial cells lining sinusoids of HCC	Hepatocytes are cytologically bland; endothelial cells are prominent and pleomorphic; in HCC endothelial cells are inconspicuous; spindle cells and cavernous foci may be present	+CD34, other endothelial markers in pleomorphic endothelial cells
Other Sarcoma	Bland to pleomorphic spindle cells with or without differentiated sarcoma elements can be present in HCC (sarcomatoid variant, carcinosarcoma)	For diagnosis of HCC, need to demonstrate differentiated foci	+CK, AFP would favor HCC; otherwise, not helpful

been reported as a common feature of hepatitis C, in the current study the degree of fatty changes was usually minimal and its absence was not unusual. Recent data suggest that fatty change varies with genotype of virus[20] and other contributions.

As a practical matter, biopsies taken in hepatitis B and C are generally done for the purpose of grading and staging of disease, not for diagnosis. Clinical, LFT, serologic tests usually set the diagnosis. The result of the findings of HBV (ELISA, serology) should go along with HBsAg in Hepatocytes, in which the authors found good correlated results (Table 5).

The differential diagnosis of CVH includes drug reactions, autoimmune hepatitis, Wilson disease, sclerosing cholangitis, and resolving acute hepatitis[21].

Hepatitis B and C may show normal progression in the immunocompromised patient, or may progress rapidly, particularly when they recur in transplanted livers[22,23].

This virulent form of recurrent VH, often described as " fibrosing cholestatic hepatitis" is characterized by extensive hepatocellular necrosis often with prominent cholestasis and the development of pericellular fibrosis[21-23]. Often there is little inflammation. Progression is rapid with loss of the allograft. A similar process has been described in the native liver following renal transplantation, and in patients with AIDS[24,25]. The authors didn't have cases of anti-HIV +, Allograft rejection, renal transplantation. Statistical analysis for correlation in Table 6.

The authors didn't have cases of HIV + (serologic,ELISA), no case of metastasis from the other common malignancies such as primary in the breast, cervix, prostate, squamous cell carcinoma of skin and tumor from ENT sites. It could be that the

Table 13. Hepatocellular carcinoma versus metas.astatic carcinoma and cholangiocarcinoma: microscopic features useful in differential diagnosis[2,5,32]

Characteristic	Hepatocellular carcinoma	Adenocarcinoma (primary and metastatic)	Poorly differentiated carcinoma
Nonneoplastic liver	Typically cirrhotic	Cirrhosis uncommon	Cirrhosis uncommon
Growth at tumor margin	Replacement	Often sinusoidal	Often sinusoidal
Main growth pattern	Trabecular	Glands	Sheets, individual cells
Fibrous stroma	Minimal	Often prominent	Variable
Intranuclear inclusions	Common	Uncommon	Uncommon
Prominent nucleolus	Typical	Often	Variable
Tumor cell cytoplasm			
General features	Often abundant; Eosinophilic granular, clear	Variable	Variable
Bile	Occasionally present	Absent	Absent
Cu, Cu-binding protein	Occasionally present	Absent	Absent
Hyaline globules	Occasionally present	Rare	Rare
Mallory bodies	Occasionally present	Absent	Absent
Mucin	Absent	Often present	Absent
p-CEA (canalicular pattern)	Often present	Absent	Absent
m-CEA (noncanalicular)	Rarely present	Often present	?
HepPar-1	Often Present	Rarely present	?
AFP	Occasionally present	Rarely present	Absent
"Hepatocyte CK" only	Often Present	Absent	?

Table 14. Histology differential diagnosis of "chronic hepatitis"?[44]

	Disease							
Feature	Hepatitis B	Hepatitis C	Auto immune hepatitis	Primary biliary cirrhosis	Primary scelerosing cholangitis	Steato hepatitis	Wilson Disease	Mediation reaction
Portal change distribution diffuse	+	-	++	-	++ (Ductular proliferation)	-	+	+
Patchy portal infiltrate type	+	++	-	++	-	+	+	+
Lymphs	++	++ (aggregates)	++	++	++	++	++	++
Plasma cells	+	-	++	++	+	+	-	+
Eosinophil	-	-	+	+	+	-	-	+
Piecemeal necrosis	+	+	++	+	-	-	+	+
Lobular necrosis	-	-	+	-	-	+	-	+
Lobular infiltrate type or location	-	+ (lymphs) (sinusoidal)	+ (Plasma cells, With necrosis)	+ (lymphs) (sinusoidal)	-	+ (Lymphs, plasma cells) (Patchy)	-	+
Bile duct damage	+	+	+	++	+	-	-	+
Bile duct loss	-	-	-	++	+	-	-	+
Bile ductular Proliferation[a]	-	-	-	++(Patchy)	++ (Diffuse)	+	-	+
Mallory hylalin	-	-	-	+ (Late)	+ (Late)	+	+ (Late)	+
Copper accumulation[b]	-	-	-	+	+	-	+	-
Granulomas	-	- (Or rare)	-	+	-	+ (Lipogra-nulomas)		
Ground glass cells	+	-	-	-	-	-	-	+[b]

++, almost always true; +, sometimes true; -, never or very rare

[a], in precirrhotic stage

[b], because of induced endoplasmic reticulum (negative by orcein immunohistochemical stains)

liver biopsied taken only in cases ruled out of known primary, emphasis was more likely to be primary masses in liver origin or occult carcinoma with liver metastasis. IHC play the most important role in this situation for differential diagnosis. The present result reveals Hepatocyte Antigen (Hep-Par 1) to have significant correlation with HCC (Table 6) and very helpful for diagnostic usage[5,26-28].

Hep Par-1 (hepatocyte) is a relatively hepatocyte-specific monoclonal antibody that reacts with a hepatocyte epitope that is resistant to formalin fixation and tissue processing. Its staining pattern suggests organelle localization, possibly mitochondrial. Studies from the University of Pittsburgh in Pennsylvania have shown performance characteristics similar to those of p-CEA, with 82% sensitivity and 90% specificity. Hep Par-I has been shown to be useful for distinguishing HCC from cholangiocarcinoma and metastatic adenocarcinoma in most settings, although positivity is occasionally found in cholangiocarcinoma[29]. Hep Par-I is probably the best[5] used as part of a panel of immunomarkers (Table 10, 11).

The authors didn't apply the proliferating markers (Ki-67), which a few studies suggest benefit to consider proliferative capacity, low to high grade dysplastic nodules, according to the definition of the International Working party [30,31]. The dysplastic foci, LCC, RN, "nodule-in-nodule" are interesting and found close to nearby malignancy[5,32].

Factors implicated in the Pathogenesis of HCC are shown in Table 22, The possible evolution of HCC in CLD has been suggested as in Fig. 44. Classification of Primary hepatic neoplasms,Preneoplastic, Dysplastic and Nonneoplastic masses demonstrate in Table 15-22.

Conclusion

The final surgical pathology diagnosis from 66 patients has represented us the clinical and laboratory investigation point of views. The differential diagnosis, added pathologic study tests (histochemistry, IHC, PEP, EM). Histopathologic reviewed had been made for final diagnosis.

The authors found correlation in findings of HBsAg (serology and IPX) in CH, LC, HCC. Although anti HCV + does not correlate, probably this is a small sample size study in one year period. In the update knowledge, HBV, HCV, and also other non B-non C play an important roles causing CLD, LC, HCC. The most helpful IHC to confirm malignant tumor to be HCC is Hepatocyte antigen (Hep-Par 1). The authors found several rare cases, but very interesting from

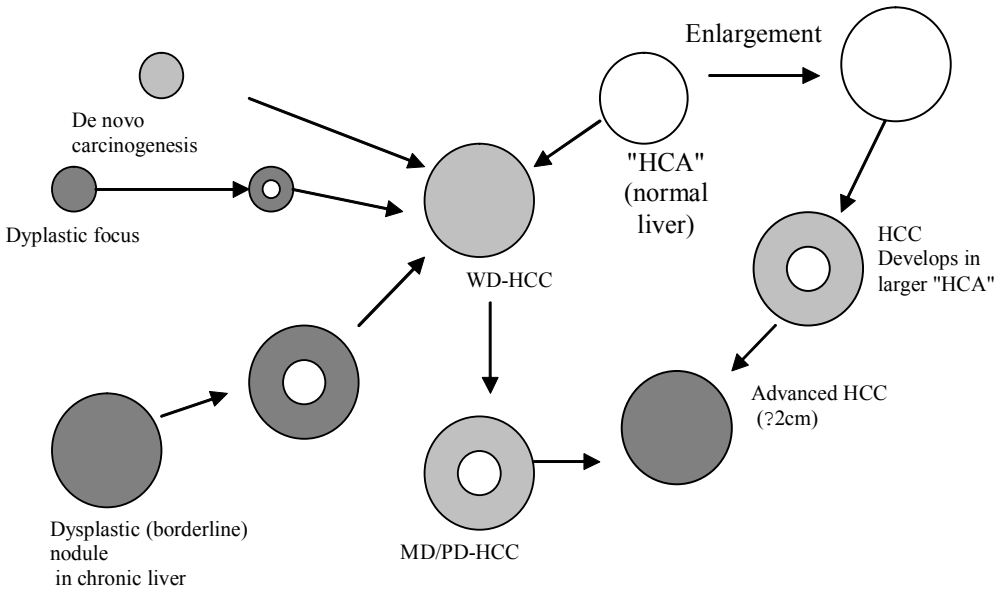

Fig. 44 Possible evolution of hepatocellular carcinoma (HCC) in chronic liver disease or cirrhosis and in the normal liver. Whether HCC developing within dysplatic nodules in the context of chronic liver disease represents the major pathway to HCC is unknown. A "nodule-in-nodule" pattern is common, with foci of well-differentiated HCC arising centrally in a clone like manner, subsequently replaced in lesions larger than 1 cm by moderately differentiated (MD) or poorly differentiated (PD) HCC. As in chronic liver disease or cirrhosis, HCC in the normal liver could arise de novo or from a dysplastic focus. Hepatocellular adenoma (HCA) or adenoma-like lesions (possible grade1 HCC) could provide fertile soil for the development of some cases[30,31]

Table 15. Classification of primary hepatic neoplasms and nonneoplastic masses[5,32]

Benign	Malignant
Epithelial	Epithelial
Hepatocellular	Hepatocellular
Hepatocellular adenoma	Hepatocellular carcinoma
Focal nodular hyperplasia	Fibrolamellar variant
Nodular regenerative hyperplasia	Combined hepatocellular carcinoma-cholangiocarcinoma
Macroregenerative nodule	Hepatoblastoma, epithelial type
Dysplastic (borderline) nodule	
Compensatory lobar hyperplasia	
Accessory lobe	
Cholangiocellular	Cholangiocellular
Bile duct hamartoma (von Meyenburg complex)	Cholangiocarcinoma
Bile duct adenoma	Intraductal variant ("biliary papillomatosis")
Biliary cysts (nonneoplastic)	Cholangiocellular carcinoma
Solitary	Adenosquamous carcinoma
Polycystic disease	Mucoepidermoid carcinoma
Caroli disease	Squamous cell carcinoma
Multiple hilar cysts	Combined cholangiocarcinoma-neuroendocrine tumor
Biliary cystadenoma	Biliary cystadenocarcinoma
Mucinous (with or without mesenchymal stroma)	
Serous	
Mesenchymal	Mesenchymal
Vascular	Vascular
Hemangioma	Angiosarcoma
Infantile hemanguioendothelioma	Epitheiod hemangioendothelioma
Hemangiomatosis	Kaposi sarcoma
Lymphangioma (-tosis)	
Hereditary hemorrhagic telangiectasia	
Peliosis hepatis	
Fatty tumors	Fatty tumors
Angiomyolipoma (and related tumors)	Liposarcoma
Pseudolipoma	
Focal (hepatocellular) fatty change	
OtherOther	
Solitary fibrous tumor	Embryonal (undifferentiated0 sarcoma
Inflammatory myofibroblastic tumor (pseudotumor)	Rhabdomyosarcoma
Leiomyoma	Fibrosarcoma, malignant fibrous histiocytoma
Leiomysarcoma	
Osteosarcoma	
Mixed epithelial and mesenchymal	Mixed epithelial and mesenchymal
Mesenchymal hamartoma	Mixed hepatoblastoma
Sarcomatoid carcinoma (carcinosarcoma)	
OtherOther	
Necrotic/fibrous nodule	Malignant schwannoma
Heterotopia (adrenal,,pancreas,spleen)	Germ cell tumors (teratoma, yolk sac tumor)
Endometas.rial cyst (endometas.rioma)	Malignant rhabdoid tumor
Benign nerve sheath tumors	Primary lymphoma
Sarcoid pseudotumor (sarcoidoma)	Primary neuroendocrine neoplasm
Abscesses	Pheochromocytoma
Parasitic cysts	Solid and cystic tumor
Ciliated foregut cyst	
Alimentary duplication cysts	
Pseudocysts (pancreatic, traumatic)	

Table 16. Relative prevalence rates of primary hepatic tumors in the general and pediatric populations in the United States[33]

Tumor type	General population (%)	Pediatric population (%)
Malignant (total)	(94)	(55-68)
Hepatocellular carcinoma	82	19-20
Hepatoblastoma	1	26-36
Cholangiocarcinoma	10	-
Angiosarcoma	<1	≤2
Embryonal sarcoma	<1	7-9
Other malignant tumors	<1	≤1
Benign (total)	(6)	(32-45)
Infantile hemangioendothelioma	-	18
Hepatocellular adenoma	1	2-4
Focal nodular hyperplasia	3	3-10
Nodular regenerative hyperplasia	-	0-5
Mesenchymal hamartoma	-	8
Other benign tumors	2	-

Table 17. Cystic masses of the liver[3,5,32,34-37]

Classification	Diagnostic Findings
Abscesses	
Amebic	Cavities filled with odorless necrotic hepatic tissue (anchovy sauce); neutrophils rare or absent; trophozoites at periphery, do not mistake for histiocytes; reactive hepatocytes may be present; PAS and iron hematoxylin stains may be helpful
Pyogenic	Cavities filled with foul-smelling necrotic hepatic tissue containing many neutrophils; often polymicrobial; Escherichia coli most common; anaerobes frequently isolated
Parasitic (echinococcal) cysts	Echinococcus granulosus: unilocular cysts (three layers) often with daughter cysts; broad capsules; protoscolices with attached or detached acid-fast birefringent hooklets
Nonparasitic(nonneoplastic)cysts	
Solitary (unilocular)	Typically, cuboidal flattened, biliary type epithelial lining; rarely squamous; thin fibrous wall; found in < 1% of routinely performed autopsies
Fibropolycystic disease	
Adult polycystic disease (ADPKD)	Typically multiple cysts and autosomal dominat inheritance; prevalence of 0.15% at autopsy; associated with adult polycystic kidney disease in 71% to 93% of cases; rarely,liver is massively enlarged; histologically similar to solitary type
Caroli disease	Ectatic intrahepatic bile ducts, inspissated bile with or without hepatolithiasis, cholangitis
Caroli syndrome	Caroli disease plus congenital hepatic fibrosis
Condenital hepatic fibrosis/ARPKD	Angulated bile ducts often with inspissated bile in fibrotic portal tracts with portal-portal bridging fibrosis; only rarely macroscopic hepatic cysts
Multiple hilar cysts	Noncommunicating cysts arising from dilation of peribiliary glands typically in hilum; often associated with cirrhosis, portal vein thrombosis; common in patients with ADPKD
Mesenchymal hamartoma	Solid and cystic mass, 75% ≤1 y of age; admixture of nonneoplastic tissue types (myxoid stroma, hepatocytes, bile ducts; blood vessels); association with translocation involving chromosome 19q;rare association with embryonal sarcoma
Alimentary tract-related cysts	Intrahepatic ileal and duodenal duplications and ciliated foregut cyst described
Pseudocysts (trauma, ischemia, pancreatic origin)	Fibrous lining; may contain blood 9mematoma0, bile (biloma)
Neoplastic cysts	Biliary cystadenoma/cystadeno carcinoma
Mucinous type	Most common type of multilocular cyst, but only 5% of all solitary cysts; 95% occur in women; lined by columnar-cuboidal mucin containing epithelium; spindle-cell stroma (85%) in women, search carefully for dysplasia (borderline lesion), cystadenocarcinoma; rule out metastasis from other primary site 9pancras, ovary, appendix0
Serous (microcystic, glycogen-rich) type	Very rare; multiocular, bland, flattened to cuboidal cell lining; clear glycogen-rich, mucin-negative cytoplasm; no spindle-cell stroma; rule out metastasis from pancreas
Teratoma	Derivatives from three germ layers; problem of "teratoid hepatoblastoma"
Other	Cystic degeneration of various neoplasm

Table 18. Clinical and pa thologic features helpful in the differential diagnosis of benign and malignant hepatocellular tumors in adults and children[5,32]

Features	Associated Cirrhosis/Chronic Liver Disease					
	Absent				Present	
	Hepatocellular Adenoma	Focal Nodular Hyperplasia	Nodular Regenerative Hyperplasia	Fetal Hepatoblastoma	Macroregenerative Nodule	Usual Hepato-cellular Carcinoma
Clinical						
Peak age (decade)	Third to fourth	Third to fourth	Fifth to seventh	First (90% < 5 y)	Fifth to sixth	Sixth to seventh (USA)
Male-to-female retio	1:15	1:6-15	1:1	2:1	2-3:1	3-4:1 (USA)
Usual presentation	Acute abdominal pain	Asymptomatic	Portal hypertension	Abdominal mass	Screening for hepatocellular carcinoma	Abdominal pain, mass; screening
Associated conditions	OCS use (85%-90%) androgens, metabolic disorders	OCS use (66%-95%) cavernous hemangioma multiple focal nodular hyperplasia syndrome	Connective tissue disease, myelolymphoprolif erative disorders, drugs/toxins, vascular disorders, other	5% congenital anomaly, familial adenomatous polyposis	-	-
Serum α-fetoprotein	Normal range	Normal range	Normal range	90% elevated	Normal range or range of CLD	60%-80% elevated
Macroscopic						
Number of nodules	70%-80% single	70%-80% single	Numerous	70%-80% single	Usually > 1	Usually > 1
Nodule diameter	75% ?10 cm	75%-80% <5 cm	0.1-4+ cm	50% 10-12 cm	90% < 1.5 cm	Variable
Cut surface often	Tan-white, often hemorrhagic	Tan, nodular, rarely hemorrhagic or dilated vessels	Tan-white, rarely hemorrhagic	Tan-brown, green necrotic	Similar to adjacent liver; may be paler or bile stained	Tan-gray, green, necrotic
Fibrous septa/scar	Rare	Usually present	Absent	Absent	Absent	Absent
Microscopic						
Portal tracts	Absent	Absent	Present with or without portal venopathy	Absent	Present, often distorted	Absent
Hepatocyte plate thickness	1-2 cells (sheetlike)	1-2 cells	1-2 cells	2-3 cells, alternating light/dark pattern	1-2 cells	Typically > 3 cells
Nuclear atypia						
Mitoses	Rare	Absent	Rare	Absent or rare	Absent	Present
Septa (arteries, bile ductules, inflammation; few portal veins, bile ducts)	Absent or rare Absent	Absent Present	Absent Rare (large nodules)	Rare or absent Absent	Absent May be present	Common Absent
Nontriadal (intranodular) arteries	Common	Absent or rare	Rare (large nodules)	-	Absent or rare	Common
Hepatocytes inside and outside nodule vary in size, plate arrangement	Absent	Absent	Present	Absent	Possible	Absent

this current study (Amyloidosis, secondary hemochromatosis, Echinococcus cyst, PCD of liver etc.).

The clinical and histopathologic study with IHC are necessary to make the final diagnosis in Masses of the liver to be primary tumor, metastatic tumor, tumor-like lesions (Pseudotumor). Borderline nodules (Dysplastic nodules) also worth studying in details prior to making a diagnosis. Nonneoplastic liver disease consists of many interesting lesions: 7 cases of pseudotumor, with clinical and radiographic findings mimic liver tumor.

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Abbreviations

A_1AT = α - antitrypsin
A_1ACT = α -antichymotrypsin
ADPKD = Autosomal-dominant polycystic kidney disease
ARPKD = Autosomal-recessive polycystic kidney disease
AFP = α - fetoprotein
AST = Asparpate aminotransferase/SGOT
ALB = Albumin
ALT = Alanine aminotransferase/SGPT
ALP = Alkaline Phosphatase
Anti HIV = Antibody to human immunodeficiency virus
Anti HCV = Antibody to Hepatitis C virus
Anti HBS = Antibody to Hepatitis B virus
CA = Cancer/Carcinoma
CAH = Chronic active hepatitis
CA 125 = Cancer antigen 125
CA 19-9 = Cancer antigen 19-9
CC = Cholangiocarcinoma
CH = Chronic hepatitis
CEA = Carcinoembryonic antigen
CPH = Chronic persistent hepatitis
CLD = Chronic liver disease
CK = Cytokeratin
CVH = Chronic viral hepatitis
Cu = Copper
CG = Chromogranin
DB = Direct bilirubin
DR = Diastase resistant
EM = Electron microscopy
EMA = Epithelial membrane antigen
ERY-1 = Erythropoiesis-associated antigen
ENT = Ear, nose, naso-pharynx, throat
ELISA = Enzyme-linked immunosorbent assay
F = Female
FNH = Focal nodular hyperplasia
GIST = Gastrointestinal Stromal Tumor
HBV = Hepatitis B
HBsAg = Hepatitis B surface antigen
HBcAg = Hepatitis B core antigen

Table 19. Nodular regenerative hyperplasia: associated conditions[32,44-47]

Immunologic disorders
Connective tissue diseases
Rheumatoid arthritis with or without Felty syndrome
Systemic lupus erythematosis
Progressive systemic sclerosis
Raynaud phenomenon
Glomerulonephritis
Cryoglobulinemia
Common variable immunodeficiency
Autoimmune hemolytic anemia
Myasthenia gravis
Hyperthyroidism or hypothyroidism
Idiopathic thrombicytopenic purpura
Neoplastic disorders
Myeloproliferative disorders
Lymphoproliferative disorders
Primary and secondary hepatic carcinomas
Drugs and toxins
Azathioprine
Chemotherapeutic agents
Toxic oil syndrome (? Adulterated rapeseed oil0
Arsenic
Vinyl chloride
Corticosteroids
Anabolic steroids
Contraceptive steroids
Vascular disorders
Obliterative portal venopathy
Extrahepatic portal vein thrombosis
Arteritis
Hepatic venous outflow obstruction
Peliosis hepatitis
Primary pulmonary hypertension
Transplantation
Kidney, bone marrow, liver, heart
Miscellaneous disorders
Precirrhotic primary biliary cirrhosis and other chronic liver diseases
Idiopathic portal hypertension and related disorders
Generalized mastocytosis
Sarcoidosis
Tuberculosis
Krabbe disease
Down syndrome

Table 20. Nonmalignant hepatocellular nodules in the cirrhotic liver: preferred terminology with related terminology from the literature[30,43]

Macroregenerative (or large regenerative) nodule
Macroregenerative nodule, type I
Ordinary macroregenerative nodule
Hepatocellular pseudotumor
Dysplastic (borderline) nodule
Macroregenerative nodule, type II
Atypical macroregenerative nodule
Atypical adenomatous hyperplasia
Normotrabecular hepatocellular carcinoma
Hepatocellular carcinoma, grade 1 (Edmondson, Steiner)

HCA	=	Hepatocellular adenoma
HCC	=	Hepatocellular carcinoma
HCV	=	Hepatitis C
H&E	=	Hematoxylin and Eosin
Hep-Par 1	=	Hepatocyte paraffin 1
HMB	=	Human melanoma black
HMFG	=	Human milk fat globulin
IHC	=	Immunohistochemistry
IPX	=	Immunoperoxidase
Ki-67antigen	=	Antibody to cell proliferation related antigen
LC	=	Liver cirrhosis
LCC	=	Large cell change or large cell dysplasia
LFT	=	Liver function test
LN	=	Lymph node
m	=	monoclonal
M	=	Male
MD	=	Moderately differentiated
Metas.	=	Metastatic
MSA	=	Muscle-specific actin
NRH	=	Nodular regeneration hyperplasia
NE	=	Neuroendocrine tumor
OCS	=	Oral contraceptive steroids
p	=	polyclonal
PAS	=	Periodic Acid-Schiff
PBC	=	Primary biliary cirrhosis
PCD	=	Polycystic disease
P-CEA	=	Polyclonal-carcino embryonic antigen
PD	=	Poorly differentiated
PEP	=	Protein electrophoresis
PSA	=	Prostate-Specific Antigen
PSAP	=	Prostate-Specific Acid Phosphatase
PTHrP	=	Parathyroid hormone-related peptide
RN	=	Regenerating nodule
SMA	=	Smooth muscle actin
SYN	=	Synaptophysin
TB	=	Total bilirubin
VH	=	Viral hepatitis
WD	=	well differentiated

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Table 21. Histologic features useful in differential diagnosis of benign, borderline (dysplastic), and malignant hepatocellular nodules typically arising in the cirrhotic liver[30,31]

Histologic Features	Macroregenerative Nodule	Dysplastic Nodule		WD-HCC	MD-HCC
		Low Grade	High Grade		
Primary diagnostic utility					
Mitoses, at least moderate (>5/10 PF)	-	-	-	-	+
Hepatocellular plates >3 cells thick	-	-	-	-	+
Reticulin uniformly <normal	-	-	-	-	+
Positive endothelial markers (endothelium)	-	-	?	+/-	+
Uniformly prominent nucleoli	-	-	-	-	+
Nuclear density >2X normal	-	-	-	+	+
Irregular nuclear contour, e" moderate	-	-	-	+	+
Nuclear hyperchromasia	-	-	+	+	+
Intranodular (nontriadal) arteries	-	+	+	+	+
Subpopulations ("clonelike")	-	+	+	+	+
Secondary diagnositc utility					
Invasion of stroma or portal tracts	-	-	-	+	+
Mitoses, few (1-5/10 PF)	-	+	-	+	
Nuclear density >1.3X normal	-	-	+	+	+
Irregular nuclear contour, mild	-	-	+	+	+
Pseudoglands	-	+	-	+	
Cytoplasmic basophilia/clear cell change	-	-	+	+	+
Resistance to iron accumulation in iron-loaded ("iron-free foci")	-	?	+	+	+

Table 22. Factors implicated in the pathogenesis of hepatocellular carcinoma[4,46,47]

- Chronic hepatic injury (60-90%)
  - Cirrhosis (most common)
  - Chronic hepatitis only (far less common) (hepatitis B >> hepatitis C)
- Specific causes
  - High rate of associated HCC (> 15%)
    - Hepatitis B
    - Hepatitis C
    - Hereditary hemochromatosis
    - Hereditary tyrosinemia
    - Porphyria cutanea tarda
    - Hypercitrulinemia
    - Membranous obstruction of the inferior vena cava
  - Intermediate rate of associated HCC (5-15%)
    - Alcohol ingestion
    - α_1-Antitrypsin deficiency
    - Glucogen storage disease (types 1 and 3)
    - Autoimmune hepatitis (?)
  - Low rate to rare presence of associated HCC (< 5%)
    - Primary biliary cirrhosis
    - Primary sclerosing cholangitis
    - Hereditary fructose intolerance
    - Paucity of intrahe[atic bile ducts
    - Progressive intradepatic cholestasis (Byler disease)
    - Congenital hepatic fibrosis
    - Biliary atresia
    - Wilson's disease
    - Oral contraceptive steroids
    - Anabolic-androgenic steroids
    - Cardiac cirrhosis
    - Exposure to various chemicals/toxins, including afla-toxin B_1

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Appendix. Clinical & Lab Investigation of 66 patients

NO.	SEX	AGE	TP	Alb	TB/DB	AST	ALT	ALP	AFP	CEA	CA125	CA19-9	Anti HIV	Anti HCV	HBsAg	Anti HBS	HBsAg(IHC)	Hepatocyte (IHC)	CEA (IHC)	AFP (IHC)	Chronic hepatitis	Cirrhosis	HCC	SMOKING	DRINKING	RAW FISH	FINAL DX.
1	M	53	6.3	3.1	0.8/0.36	39	20	243					-				-	+	+	+	+	-	+	-	-	-	HCC(Mod.diff) gr.II,III (Lt.lobe) with bone,lung metas.
2	M	58	7.5	4.1	0.44/0.13	34	26	65	6690	1.1		2.9	-	-	+		+	+	+	+	+	+	+	+	+	-	HCC(Mod.diff) (Rt.lobe)
3	M	45											-		-		-	-	+	-	-	-	-				Metas.CA Colon (Lt. Lobe)
4	F	47			1/0.35								-	-			+				+	-	-	-	+		CH
5	F	79	7	3.3	0.3/0.13	25	17	115		2.6			-		-		-		+	-	+	+	-				CA Colon
6	F	51				26	26	70	1.7					+	-						+	-	-				CH
7	M	62	5.5	1.5	0.22/0.04	25	11	446					-								-	-	-				Amyloidosis / Necropsies
8	M	68	6.3	3.7	16-Apr	149	97	87	2.9	242	12.4	189.7	-		-	+					-	-	-				Metas. CA Rectum
9	F	49	8	4.1	0.6/0.26	28	28	74	3.8	2.9	28.6	17.2	-		-	+					-	-	-				Cavernous hemangioma
10	F	44	7.4	4.2	0.37/0.11	10		36							-			-	+	-	-	-	-				Metas.Brenner's (primary ovary)
11	F	29	8.3	3	1.39/0.77	45	163	339																			PCD (cysts)
12	F	87	8	4.1	0.59/0.11	73	67	94		558			-				-	-	+	-	-	-	-				Metas.Adenocarcinoma primary in rectum
13	M	32	7.1	4.4	3.5/2.6	142	122	335					-	+							+	+	-	-	-	-	Liver transpant,recipient, no rejection
14	F	52	8.3	4	0.32/0.07	31	12	233	1.1	1.1	12.2	69.5	-	-	-	-	-	-	+	-	+	-	-				Cholangio CA
15	F	68	6.7	2.1	1.8/1.22	81	65										-	-			-	-	-	+	+		Metas.CA primary in Lung
16	M	39	3.2	1.4	8.8/2.7	83	63	179									+	+	+	-	+	+	+				HBV,LC,Dysplasia, Early HCC
17	M	79			7.5/6.7	148	261	398		1.9		10.3									-	-	-				Metas.CA to liver,L.N. primary in Pancreas
18	F	19																			-	-	-				Acute congestion / Necropsies Liver
19	M	43	4	1.9	5.9/4.2	588	125	638					-				-				-	-	-				Acute congesion / Necropsies
20	F	27	7.5	4	0.83/0.23	142	234	64							+		+				+	-	-				CH, portal inflam.
21	M	47							1278	2.4	18.1	5.5	-	-	+		+	+		+	-	-	+				HCC Mod.diff,multinodule
22	F	51	7.1	3.1	4.5/3.9	5	96	586							-	-					-	-	-				PBC
23	M	63	7.7	2.7	0.64/0.39	65	47	167	22.6				-				-	+	+	-	-	-	+				HCC well diff
24	M	68	7.7	4.1	0.9/0.19	36	26	196	1.1	278	7.2	4000									-	-	-				Metas. CA liver (primary CA at sigmoid)
25	F	73			14.2/8.7	61	24	46													-	-	-				Secondary Hemochromatosis (Bl. Tx.)
26	M	34			1.6/0.7	80	95	372	2.2	1.3			-				-				-	-	-				GIST, metas.
27	M	59	7.9	2.7	0.88/0.19	115	72	242	25.2	1.9		14.8	-		+		+		+	+	+	+	-		+		CH, Cirrhosis, severe dysplasia (Lt.lobe)
28	M	38	7.6	3.5	0.84/0.38	59	185						-	+	-						+	-	-		+		CH
29	M	44	6	3.4	1.6/0.7	144	96	67					-				+	-	+	+	+	+	-				Meats. (primary in Stomach)
30	M	77	6.6	2.5	12.4/8.5	302	230	514					-								-	-	-				Periampullary mass, Adeno CA stomach, pancreas
31	M	38	7.3	3.6	1.08/0.53	96	47	79	350	1.8			-		+	+	+	+	+	+	+	+	+	+	+		HCC giant cell type with ruptured invade capsule, BV
32	M	30																			-	-	-				Pyogenic liver abscess
33	F	39			25.5/19.6	306	310	150						-	-	+					+	-	-				CH
34	F	49	8	4.2	1/0.5	37	90	85	3.5	2.4	15.3	46.3	-								-	-	-				PCD(Polycystic disease)

Appendix. Clinical & Lab Investigation of 66 patients

NO.	SEX	AGE	TP	Alb	TB/DB	AST	ALT	ALP	AFP	CEA	CA125	CA19-9	Anti HIV	Anti HCV	HBsAg	Anti HBS	HBsAg(IHC)	Hepatocyte (IHC)	CEA (IHC)	AFP (IHC)	Chronic hepatitis	Cirrhosis	HCC	SMOKING	DRINKING	RAW FISH	FINAL DX.
35	F	70	5.3	2.9	0.36/0.12	39	15	45	6.8		65.7										-	-	-				Metas. (primary in ovary)
36	F	41	6.5	3.1	0.55/0.25	27	18	59		4.8		47.7									-	-	-				Metas. Adeno CA (primary in sigmoid)
37	F	32	6.6	2.8	0.45/0.13	18	18	162	2.4	264	393.2	2									-	-	-				Metas. CA (primary in lung or ovary)
38	M	43	7.5	2.6	1.9/1.37	116	80	377	46.7	1.2	86.9	50.4	-	+	+		+	+			-	+	+	+	+		Liver with hyperplasia HCC
39	M	51			3.18/0.91	3610	1248	133									-	+	+	+	-	-	+				HCC with ruptured Metas. to vertebra
40	F	47							4.3	747							-	-	+	-	-	-	-		+		Metas. (unknown primary)
41	F	70			0.56/0.29	164	15	272	16.2	2.33			-								+	-	+	+	+		HCC high grade invade capsule vascular
42	M	35			2.2/0.88	123	56	372					-				-	-	+	+	-	-	-	+	+	+	Metas. Bile duct dilate
43	F	34	7.4	3.1	3.23/2.3	51	21	883			33	800	-					-	+		-	-	-				Klatskin's tumor
44	M	38															-	+	+	+	-	-	+				HCC, neoangiogenesis
45	M	26		1.9	1.3/0.9	67	12	186					-	+	+		+		+	-	+	-	-				Acute congestion, necropsies
46	F	20											-	-	-	-	-				+	-	-				CH
47	F	63	7.6	3.9	11.67/8.7	35	17	515		8.1		19635	-								-	-	-				Metas.,CA. ampulla
48	M	53	7.5	3.5		245	62	351	2.4	9.8		0.8					+	-	+	-	+	+	+		+		Metas. CA (primary in stomach)
49	M	41	6.4	3.5	1.01/0.41	140	178	43	7.4	2.7	77.7	15.6	-	+	-	+	-	+	+	-	+	+	+				HCC
50	F	46	8.1	3.7	0.52/0.17	66	45	229	95.1	7.1	72.7	15324	-	-	-						-	-	-				Metas. CA (primary in pancreas)
51	M	67	6.41	2.11	2.2/1.21	86	48	441	2.6	83.7		20000									-	-	-	+			Metas. to liver
52	F	56	7.5	3.4	1.03/0.44	13	25	266													-	-	-				Metas.,Retroperitoneal, malignancy
53	F	45	6.2	3.3	0.89/0.26	402	231	50	69	1.1	6.3	5.7	-	-	-	-					-	-	-				Ecclinococcus cyst
54	M	55							498.5				-	-	+	-	+	+			-	-	-	+	+		HCC
55	F	56							1.6	8.9	128.4	1718	-		-	+					-	-	-				Metas. Mucinous adeno CA (primary in ovary, Rt. Adnexa)
56	F	63	6.4	2.9	3/1.9	102	39	429	463								+	+	+	+	+	+	+	+	+		HCC
57	M	63																			+	-	-				CH, nonspecific
58	F	61							48	7.2	15.2	8.9									-	-	-	+			Solitary cyst of liver
59	F	89	7.8	4	0.7/0.2	34	12	86													-	-	-				(PCD)Cyst of liver,Kidney
60	M	43																			-	-	-				CC with abscess
61	F	52	7.5	2.4		36	21	232	2.1	29.3	68.4	8.1	-	-	-	-		-			-	-	-	+	+		Metas. Primary in lungs
62	M	36							0.4				-	-	+		+	+			+	-	+				HCC
63	M	23	6.4	3.3		29	54	154					-		-	+					-	-	-				Ac. Cholangiotis,stones
64	M	66	6.6	3	1.38/0.91	145	60	328													-	-	-	+	-		Metas. CA (primary in lung)
65	M	12																			-	-	-				No rejection, Liver alloyraft
66	M	37																			-	-	-				Wall of liver abcess

การศึกษาความสัมพันธ์ของไวรัสตับอักเสบบี และซี ต่อโรคตับอักเสบเรื้อรัง, ตับแข็ง และมะเร็งตับในชิ้นเนื้อตับ ณ โรงพยาบาลราชวิถี

อรุณลักษณ์ โคมินทร์, นิพนธ์ ประดิษฐผล, สุชาดา สุพรรณพยัคฆ์, รุ่งอรุณ แซ่เอี้ยว, อำไพ นุสสติ, ศุภทิพย์ ตู้จินดา, ปราณี คงธีรภาพ, สุด อินทรักษา, เรณู รักฉ่ำพงษ์, ธีระ ดีสวัสดิ์

คณะผู้วิจัยได้ศึกษาทบทวนชิ้นเนื้อตับในผู้ป่วย 66 รายที่ เข้ารับการรักษา ณ รพ. ราชวิถี ระหว่าง ธันวาคม พ.ศ. 2545 ถึง กันยายน พ.ศ. 2546 (10 เดือน) โดยมีวัตถุประสงค์ 1) หาความสัมพันธ์ระหว่าง HBV, HCV กับ CH, LC, HCC 2) เปรียบเทียบความสัมพันธ์ระหว่างการตรวจพิเศษทาง IHC โดยใช้ hepatocyte (Hep-Par1), AFP, CEA เป็น cellular markers บ่งชี้ต้นกำเนิดที่มาของเซลล์มะเร็ง ยืนยันว่าต้นกำเนิดจากเซลล์ตับ ซึ่งพบที่ตับ หรือ แผ่กระจาย 3) เพื่อศึกษาทบทวนพยาธิวิทยาของชิ้นเนื้อตับทั้ง 66 ตัวอย่าง

ผลการศึกษาพบความสัมพันธ์มีนัยสำคัญทางสถิติระหว่าง HBsAg (Serology) กับ HCC ($p = 0.010$) และระหว่าง HBsAg (IHC in liver tissue) กับ CH, LC ($p = 0.038, 0.021$ ตามลำดับ) แต่ไม่พบความสัมพันธ์อย่างมีนัยสำคัญทางสถิติระหว่าง HCV (Anti HCV positive) กับ CH, LC, HCC ซึ่งน่าจะเนื่องจากตัวอย่างศึกษาน้อยราย และระยะเวลาศึกษาไม่นาน

Hepatocyte เป็น cellular immunologic marker ที่แปลผลง่ายชัดเจนจากเซลล์ตับ หรือ เมื่อแผ่กระจายไปยังอวัยวะอื่น ๆ ($p < 0.001$) ส่วน AFP, CEA พบว่าไม่มีความสัมพันธ์อย่างมีนัยสำคัญทางสถิติกับเซลล์มะเร็งของตับ ($p = 0.999$ และ 0.670 ตามลำดับ) hepatocyte จึงมีคุณค่าอย่างยิ่งในการยืนยันการวินิจฉัยมะเร็งตับ

การศึกษา 66 ตัวอย่างได้พบโรคตับชนิดอื่นที่ไม่เกี่ยวกับไวรัสตับอักเสบ ทั้งเป็นโรคที่มีอุบัติการณ์สูง จนถึงโรคหาพบยาก, เนื้องอกของตับ และเนื้องอกอื่น ๆ รวมทั้งรอยโรคคล้ายเนื้องอก (เนื้องอกปลอม)

ผลการศึกษาความสัมพันธ์ของ HBV กับโรคตับดังกล่าว เป็นข้อมูลที่ให้ประโยชน์ สนับสนุนการฉีดวัคซีนให้เด็กเล็ก และเด็กโต หรือ ประชาชนที่ยังไม่มีภูมิคุ้มกันโดยเฉพาะบุคลากรทางการแพทย์ สาธารณสุขที่มีโอกาสเสี่ยงติดเชื้อ ซึ่งเป็นนโยบายรัฐบาลไทยโดยกระทรวงสาธารณสุขได้ดำเนินการมาตั้งแต่ พ.ศ. 2535 ในแผนฉีดวัคซีนป้องกันโรคระดับชาติ และกำลังดำเนินอยู่อย่างต่อเนื่อง