A Morphological Study of Histological Activity Index (HAl) and Scoring System in Hepatitis-C

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Sajid Mushtaq, Muhammad Muzaffar, Muhammad Tahir Khadim, Waheed-Uz-Zaman Tariq, Nadim Mamoon (Armed Forces Institute of Pathology, Rawalpindi.)

Abstract

A retrospective morphological study of 25 cases of serologically positive chronic hepatitis C was carried out. Paraffin embedded sections were stained with haematoxylin, eosin and Gomori reticulin stains. The histological features were scored according to both Knodell and Scheuer systems. The results of Knodell showed 32% cases scored between 4-8 and 48% between 9-12. Cases of conventional category of chronic persistent hepatitis scored between 1-3 and chronic activehepatitis score ranged between 4-12. The scoring systems provide a good guideline for management/selection of cases for interferone therapy and sub sequent evaluation and assessment of the cases (JPMA 47:162,1997).

Introduction

Viral hepatitis is a common problem in Pakistan[1]. The most important viral agents causing chronic hepatitis are hepatitis B and C viruses[2,3]. Semmarkers are available to differentiate between hepatitis B and hepatitis C[4-6]. This differentiation is important from diagnostic, prognostic and management points of view[7-9]. Liver biopsy is an important tool for the diagnosis and management of chronic viral hepatitis[10]. It not only confirms the diagnosis, but excludes other aetiologies, provides useful information about the grade of histological activity and measures the extent of fibrosis (stage of the disease)[10-13]. Classically chronic liver disease, on histological grounds is classified mainly as chronic persistent (CPH), chronic active (CAH) and chronic lobular hepatitis (CLH)[14,15]. Chronic active hepatitis progresses to the stage of cirrhosis and chronic persistent hepatitis, a milder variant, does not progress to cirrhosis. These concepts and this classification system is considered obsolete by many hepatologists[10,11,16]. A new system of classification has been proposed. The basis of the newer system is: (a) actiology çb9) grading of activity (necroinflammatory), (c) staging[10,12-19]-
The aetiology is determined by a combination of clinical, serological, biochemical and histological parameters. The grading and stagin of the disease relies solely upon histological features[8,20]. In order to assess these features semi-quantitative histological activity index/scoring systems have been introduced[5,19] . The two commonly used scoring systems are those of Knodell[17] and Scheuer[16]. These scoring systems assign numbers to different histological parameters and provide a numerical assessment of the activity[10,16,17,19]. This study evaluates and compares the new scoring systems with the conventional classification systems in the morphological diagnosis of chronic hepatitis C.

Material and Methods

Liver biopsy specimens for histological examination were obtained from 25 cases of chronic hepatitis C. Liver biopsy was done due to persistence of symptoms, raised serum transaminases or positive serology for hepatitis C. The serology for hepatitis C was done by second generation ELISA at Armed Forces Institute ofPathology.

Biopsies were fixed in 10% buffered fonnalin. Five mm thick sections were stained with haematoxylin, eosin and reticulin stains. Histological diagnosis was made using the conventional criteria for chronic persistent hepatitis (CPH), chronic active hepatitis (CAH) and chronic lobular hepatitis (CLH). The scoring was done according to Knodell and Scheuer histological activity index/scoring system. Briefly this was based on the assessment of portal/periportal activity with or without bridging necrosis, intralobular necrosis, portal inflammation and fibrosis. In Knodell scoring, the score was assigned out ofa total sum of 22 including the score forextent of fibrosis (stage). Many histopathologists do not include fibrosis (fibrosis/score range 0-4) as part of grading inKnodell system and it is considered to reflect the stage of the disease process10,12 According to the total score the lesions are divided into 4 groups. Group I score between 1-3, Group II score 4-8, Group III score 9-12 and Group IV score between[13-18].

All biopsies were scored by three observers independently, after an interval of few months by one of the authors. Two way ANOVA (analysis ofvanance) was used for inter-observer and intra- observer variation. The significant difference was takenat $P<0.05$. The calculated Pvalues did not show any significant inter or intra observer variation (Micro state-il, version I, copyright C, 1988 Ecosoft Inc).

Results

Of 25 cases there were 18 males and 7 females whose average age was 40 years. The common presentation was generalized weakness/malaise, impaired liver function tests and jaundice. There were 6 (24%) asymptonlatic cases with past history of altered liver function tests. According to the conventional classification there were 2 cases of CPH, whose knodell HAl ranged between 1-3 (Figure 1 and 2)

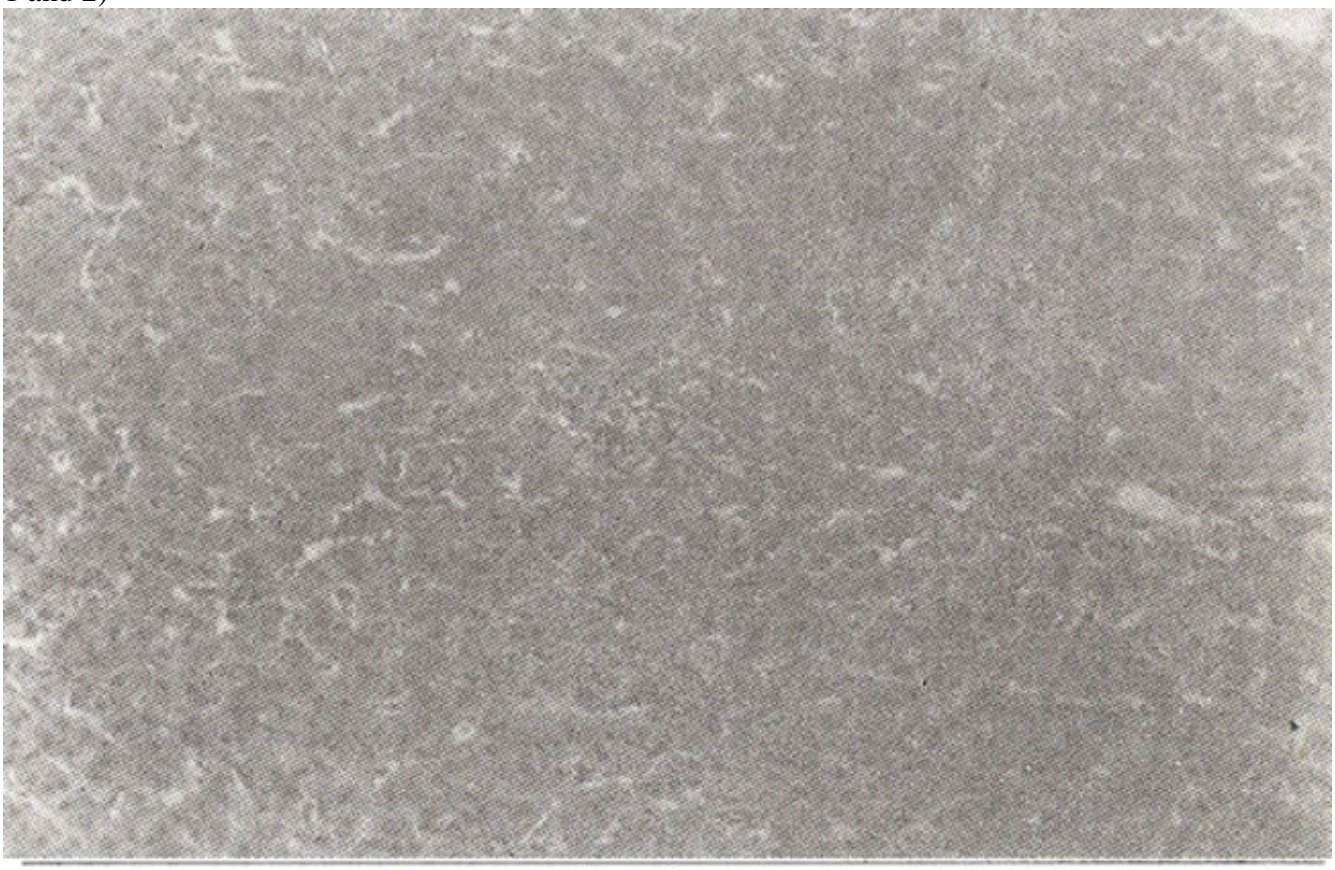

Figure 1. Chronic hepatitis C with mild activity. Knodell HAI Score - 2/22.

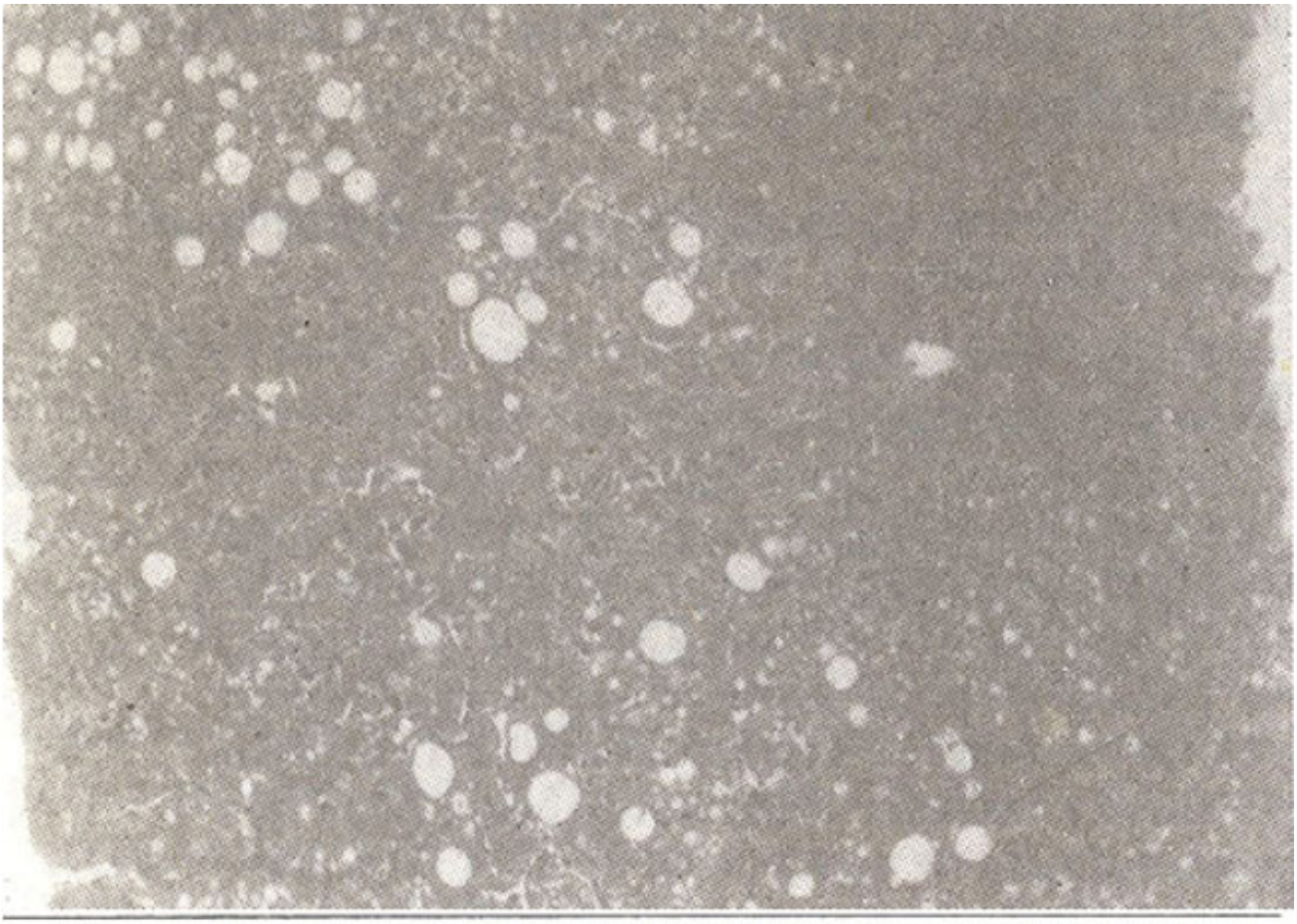

Figure 2. Chronic hepatitis C with mild activity. Knodell HAI sCORE - 2/22.

and one case of chronic lobular hepatitis had a HAl score of 2. Of 22 cases with CAT-I. 7 had CAR with developing cirrhosis and Knodell score in these ranged from 4-8 (Figure 3);

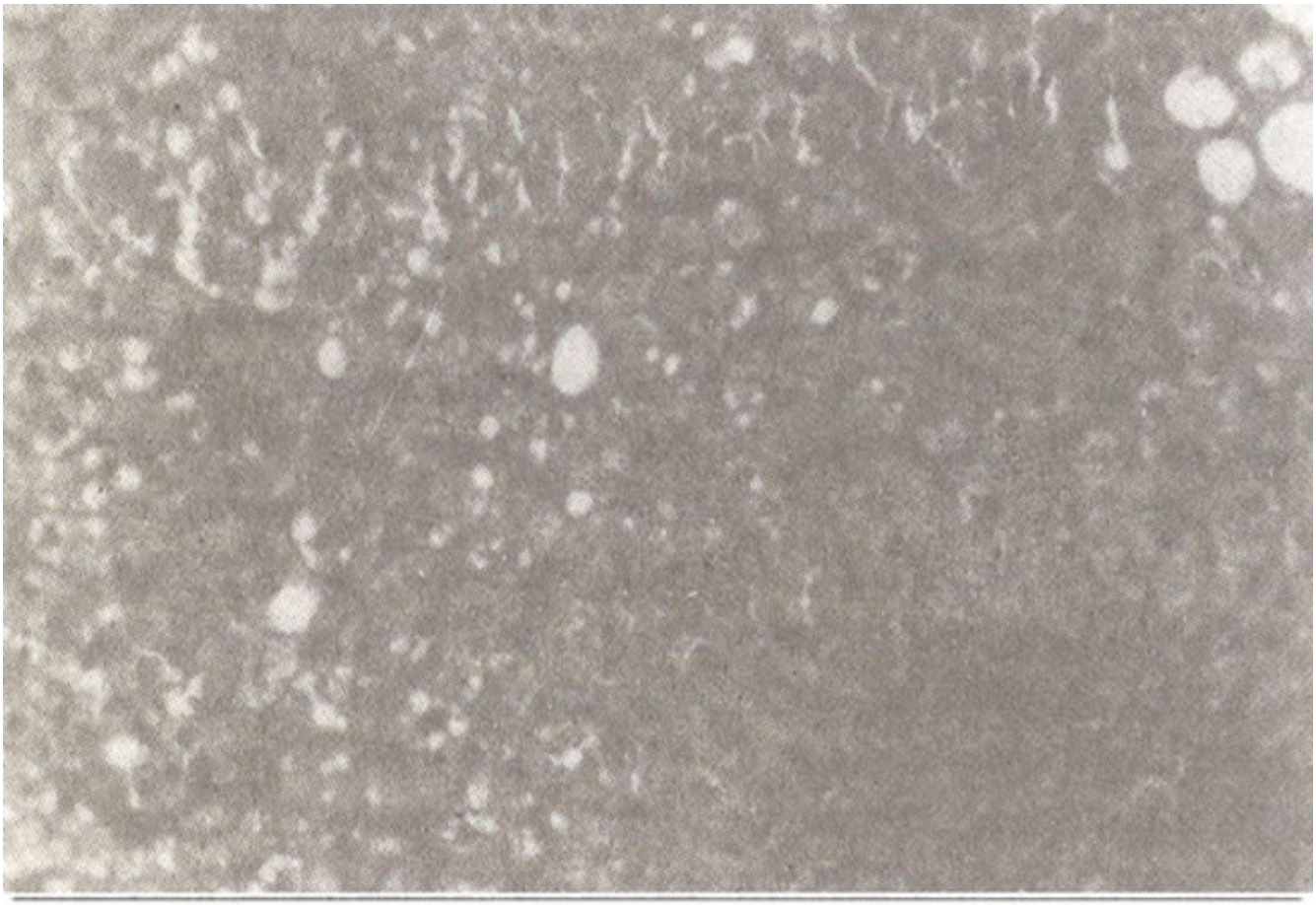

Figure 3. Chronic hepatitis C with moderate activity. Knodell HAI Score - 6/22.

of 8 cases with CAR cirrhosis, had variable extent of fibrosis and Knodell score in these cases was more than 9 (Figure 4).

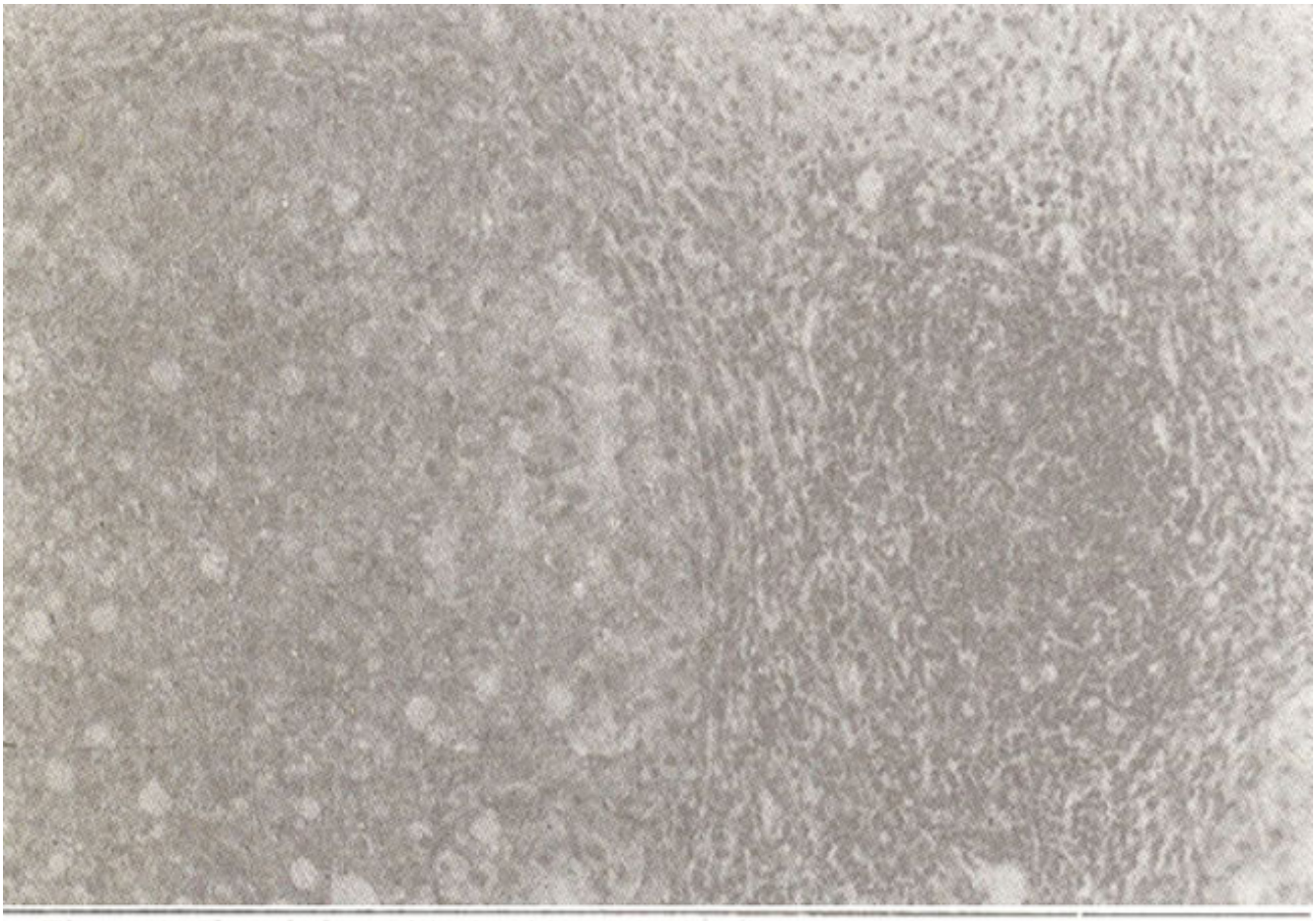

Figure 4. Chronic hepatitis C with marked activity. Knodell HAI Score - 13/22.

The results of Knodell scoring system are presented in (Table I).

Table I. Knodell histological activity index (HAI).

HAI	Number	Percentage
1-3 (Group I)	3	12
4-8 (Group II)	8	32
9-12 (Group III)	12	48
13-18 (Group IV)	2	8

According to the total score, the cases were divided into four groups. Largest number of cases (48%) was-seen in group III. The results of individual parameters used for grading are shown in Table II.

Table II. Knodell histological activity index (HAI).

	Score (0-10)	No. of cases	%
A. Periportal necrosis (PN) with or without bridging necrosis			
a. None	(0)	-	-
b. Mild piecemeal necrosis	(1)	2	8
c. Moderate PN(<1/2 cirum)	(3)	4	16
d. Marked PN (>1/2 cirum)	(4)	11	44
e. Moderate PN + Bridging necrosis	(5)	3	12
f. Marked PN + Bridging necrosis	(6)	3	12
g. Multi-lobular necrosis	(10)	2	8
B. Intralobular degeneration and focal necrosis			
a. None	(0)	2	8
b. Mild (1/3 of lobular)	(1)	11	44
c. Moderate (1/3 - 2/3)	(3)	10	40
d. Marked (> 2/3)	(4)	2	8
C. Portal inflammation			
a. None	(0)	-	-
b. Mild (<1/3 of portal tract)	(1)	3	12
c. Moderate (1/3-2/3)	(3)	17	68
d. Marked (>2/3)	(4)	5	20
D. Fibrosis			
a. None	(0)	2	8
b, Fibrous portal expansion	(1)	12	48
c. Bridging fibrosis	(3)	3	12
d. Cirrhosis	(4)	8	32

Accordingto the Knodell scoring system, majority of the cases (48%) fell in the category of chronic hepatitis with severe activity and fibrosis, whose score ranged between 9-12 (Figure 4). Periportal necrosis was assigned a score of 0 to 10 (Table II-A). Majority of cases showed severe piecemeal necrosis and therefore, were assigned a score of 4. When accompanied by bridging necrosis, the score

increased to 06 in other cases. Intralobular degeneration (Table II-B) was mild in the majority (44%) of these cases and they were given a score of 1. Portal inflammation assessed by the degree of chronic inflammatoiy infiltrate in portal tracts was assigned a score from 0 to 4 (Table II-C). Majority of cases (68%) showed moderate degree of inflammation and were given the score of 3. Fibrosis is the determinant of the stage of disease and was classified into 04 groups (Table II-D). Some degree of fibrosis was present in 23/25 cases (Figure 5).

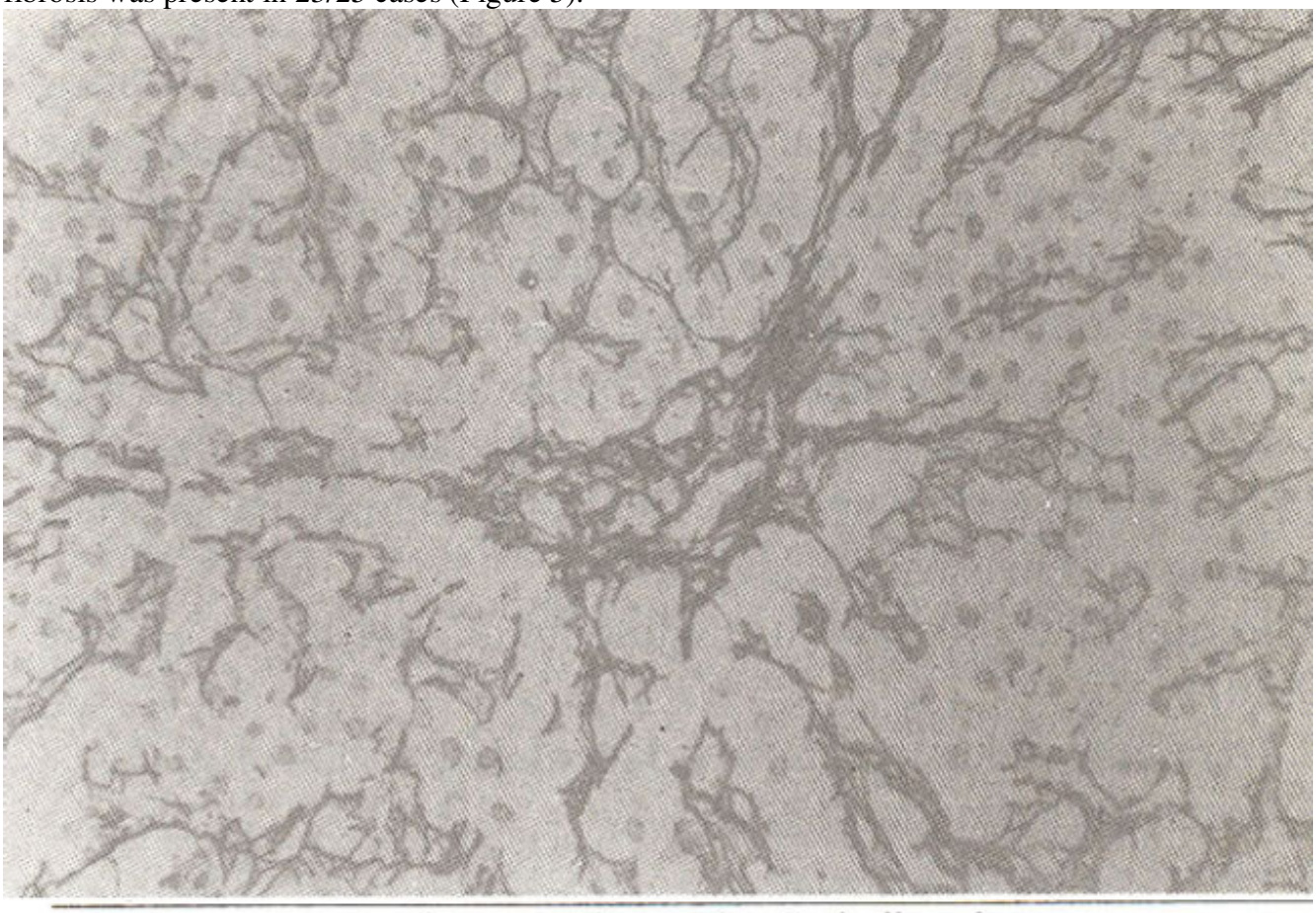

Figure 5. Fibrous portal expansion. Reticulin stain.

Eight of these had fully developed cirrhosis and were given the score of 4. According to the Scheuer histological activity index,/scoring system, a total score of 12 was assigned. Using this system the portal periportal activity was scored between 0-4. Majority (15%) showed moderate piecemeal necrosis and scored 3. The lobular activity was assigned scores ranging between 0-4 and similar scoring was done for the extent of fibrosis (Table III).

Table III. Scheuer histological activity index (HAI).

	Score (0-4)	No. of cases	%
I. Portal/Periportal activity			
a. None/minimal	(0)	-	-
b. Portal inflammation CPH	(1)	3	12
c. Mild PN (moderate CAH)	(2)	4	16
d. Moderate PN (moderate CAH)	(3)	15	60
e. Severe PN (severe CAG)	(4)	3	12
II. Lobular activity			
a. None	(0)	2	8
b. Inflammation no necrosis	(1)	5	20
c. Focal necrosis/Acidophil boding	(2)	11	44
d. Severe focal cell damage	(3)	2	8
e. Damage includes bridging necrosis	(4)	5	20
III. Fibrosis			
a. None	(0)	2	8
b. Enlarged, fibrotic portal tracts	(1)	7	28
c. Periportal or portal portal septa	(2)	4	16
d. Fibrosis, architectural distortion. No cirrhosis	(3)	4	16
e. Probable/definite cirrhosis necrosis	(4)	8	32

Correlation between conventional nomenclature! classification of chronic hepatitis was done with the Knodell histological activity index score (Table IV).

Table IV. Correlation between conventional nomenclature of chronic hepatitis and semi-quantitative grade/score (n=25).

Conventional diagnosis	HAI score	Number	%
Chronic persistent hepatitis	1-3	2	8
Chronic lobular hepatitis	2	1	4
Chronic active hepatitis with mild activity	4-8	8	32
Chronic active hepatitis with moderate activity	9-12	12	48
Chronic active hepatitis with marked activity.	13-18	2	8

Discussion

Chronic viral hepatitis is a common problem in Pakistan[1,2,21,22]. Several studies perfonned in Pakistan before the availability of seromarkers for hepatitis - Chad shown that majority of the cases were not due to hepatitis A or B virus. The carrier state of hepatitis B (HBs Ag) is 8-10%, whereas antibodies against HBs Ag (anti HBs) and anti HBC are present in 17% and 40-50% of Pakistani population respectively[1,23]. The preliminary reports indicate 43% sempositivity for hepatitis C in chronic liver disease; 18% in cirrhosis and 61% in hepatocellular carcinoma[2]. In another study of chronic liver disease, anti HCV was positive in 25% patients[1]. According to the conventional classification of chronic hepatitis the cases are categorised as CPH, CAH and CLH. This classification was proposed at a time when the entity of Hepatitis C and other etiological factors were not known[14,27]. During the last two decades there has been an impressive advancement in the understanding of chronic hepatitis including the identification of etiological factors such as hepatitis B,C,D, autoimmunity, various dmgs effects on the liver along with tremendous advances in the treatment[6,18,24]. The treatment of the chronic hepatitisvaries according to the etiological agent. Better understanding of the etiology and pathogenesis of chronic hepatitis had changed the concept of classification, from purely histological to a more elaborate version with the combination of histological features, clinical and serological factors. The present knowledge of chronic hepatitis calls for a revised classification to incorporate the available information about these clinical and histopathological syndromes of chronic hepatitis[10,11]. The new classification incorporates etiology, grade of necroinflainmatoiy activity and stage of the disease. According to the conventional system of classification, quantitative assessment of necroinflammatory activity (grade of the disease) cannot be made, which leads to difficulties in statistical analysis. The histological activity index/scoring systems give statistical analysis with semi-quantitative measurements of the necroinflammatory activity of the disease process and provides a snap shot at that time for accurate comparison in the same case at a later stage[10,16,19]. HAl is an important requirement of therapeutic trials and is an essential supplement to the routine histological examination of liver biopsies. Them are basically four components of the scoring system used in Knodell HAl[19].

1. Periportal necrosis with or without bridging necrosis (score 0-10).

2. Intralobular degeneration and focal necrosis (score 0-4).
3. Portal inflammation (score 0-4).
4. Fibrosis (score 0-4).
Similar components constitute the Scheuer HAl also.
Only the first three parameters describe the grading of necroinflanunatoiy activity whereas, the fourth describes the stage of the disease[10,20]. Many hepatologists separate the fourth component from the first three features. The histological grade sometimes might not correlate well with the clinical and biochemical assessments. This can be due to sampling error and tendency for thç histological features to persist even after the biochemical changes revert to nonnal. Even otherwise, the precise correlation of each biochemical change with the histological features is also poorly understood[16,20-25]. We have used Knodell and Scheuer HAl system for evaluation of liver biopsies of patients of chronic hepatitis C. According to Knodell, HAl 12% caies showed scores ranging between 1-3, in 32% score ranged between 4-8 and in 48% score ranged between 9-12. According to Scheuer HAl 8% scored 1-3, 52% scored 4-8 and 40% scored 9-12. These scores of our cases show that majority of the cases had moderate to severe degree of necroinflammatory activity. The staging of chronic liver disease (CLD) is related to its time course and has an important prognostic and therapeutic role. Its histological evaluation is based on the extent offibrosis and development of cirrhosis[20]. The connective tissue stains are mandatory for staging. Twenty-eight percent of our cases showed developing cirrhosis and 32% had well developed cirrhosis. HAl alongwith the stage of the disease is required to select the cases for available therapeutic modalities. The HAl scoring is essential for further reference to evaluate the effects of therapy also.

References

1. Malik, l.A. and Tariq, W.U.Z. The prevalence and pattern of viral hepatitis in Pakistan. JCPSP, 1995;5:2-3.
2. Malik, IA., Ahmed, N., Butt, S.A. et al. The role ofhepatitis B and C viruses in the aetiology of hepatocellular carcinoma in Northern Pakistan. A preliminary report. JCPSP., 1995;5:26-28.
3. Knodell, R.G., Conrad, ME and Ishak, KG. Development of chronic liver disease after acute Non A, Non B post-transfusion hepatitia. Gastroenterology, 1977;72:902-909.
4. Zeldis, J.B., Shsbib, SM. and Tufenkeji, H. Diagnosia of viral hepatitis. Ann. SaudiMed., 1995;lS:1-5.
5. Bradley, D.W., Krawczynski, K., Beach, M.J. et al. Non-A, Non-B hepatitis Towards the discovery of hepatitis C and E viruses. Semin. Liver Dis., 1991;11:128-144.
6. Choo, Q.L., Kuo, 0., Weiner, A.J. et al. Isolation of cDNA clone derived from a blood borne non-A, non-B viral hepatitis genomee. Science, 1989;244:359-62.
7. Alter, N.J., Margolis, H.S., Krawezynski, K. et at. The natural history of community acquired hepatitis C in the United States. N. EngI. J. Med., 1992;327: 1899-1908.
8. Kuo, G., Choo, Q.L., Alter, N.J. et al, An assay for circulating antibodies to a major etiologic virus ofhumannon-A, non-B hepatitis. Science, 1989;244:362-364.
9. Knodell, R.G., Conrad, Mt.. Dienstag, J.L. et al. Etiological spectrum of post-transfusion hepatitis. Gastroenterology, 1975;69: 1278-1285.
10. Desmet, V.1., Gerber, M, Hoofnagle, IN. et at. Classification of chronic hepatitis: Diagnosis, grading and staging. Hepatology, 1994; 19:1513-1520.
11. Baggenstoss, A.H., Soloway, RD., Summerskill. WH.J. et al. Chronic active liver disease. The range of histologic lesions, their response to treatment and evaluation. Hum. Pathol., 1972;3:183-198.
12. Scheuer, P.1. Liverbiopsy in chronic hepatitis 1968-1978. Gut, 1978; 19:551-557,
13. Genesca, S., Juan, L, Esteban,E etaL Blood bome Non A,Non B hepatitisC, seminars in liver

disease. Vol It, New York, ThiemeMed. Publishers Inc., 1992, pp. 147-64.
14. De-Groote, J., Desmet, V,J., Dedigk, P. etal. A classification ofchronic hepatitis. Lancet, 1968;11:626-28.
15. Ludwig, I. The nomenclature of chronic active hepatitis an obituary. Gastroen terology, 1993;105:274-278.
16. Scheuer, P.1. Classification of chronic viral hepatitis, a need for reassessment. J. Hepatol., 1991 ; 13:373-374.
17. Knodell, E.G., Ishak, KG., Craig, R. et al. Histolugy activity index for numerical scoring and assessment ofasymptomatic chronic active hepatitis liver biopsies. Gastroenterology, 1980;79: 1031-1033.
18. Geall, M.G., Schoenfield, LI. and Summerskill, W.H.J. Classification and treatment ofchronic active liver disease. Gastroenterology, 1968;55 :724-729.
19. Knodell, G.R., Ishak, KG., Black, W. et al. Formulation and application of a numerical scoring, system for assessing histological activity in asymptomatic chronic active hepatitis. Am. Assoc. Study Liver Dia., 1981; 1:431435.
20. Dhillon, A.P and Dusheiko, G.M Pathology of hepatitis C virus infection. Histopathology, 1995 ; 26:297-309.
21. Khan, A.A. Endemic transmission of hepatitis C. JCPSP, 1995;5:12-13.
22. Khan, AU., Khan, AN. and Mirza, MB. Recombinant interferon Alfa therapy in chronic hepatitis C. JCPSP, 1995;5:32-34.
23. Akram, D.S., Isomura, S. and Walla, MA. The prevalence of antibodies to hepatitis A, B and C viruses in childrenofKarachi. JCPSP, 1995;S: 17-18.
24. Davis, G.L., Balart, L.A., Schiff, ER. et al. Treatment ofchronic hepatitis C with recombinant interferon aIls: A mjslticenter randomized, controlled trial. N. EngI. I. Med., 1989;321:1501-6.
25. Scheuer, P.1., Ashraf-Zadeh, P., Sherlock, S. et al. The pathology ofhepatitis-C. Hepatology, 1992;15:567-571.
26. Mattson, L., Weilland, 0. and Glanmann, H. Application of a numerical scoring system for assessment of histological outcome in patients with chronic post-transfusion Non A, Non B hepatitis with orwithout antibody to hepatitis-C. Liver, 1990; 10:257-268.
27. Chool, DL., Kuo, G., Weiner, A. et al. Identification ofthe major, parentral Non A, Non B hepatitis agent (Hepatitis C) using a recombinant c DNA approach. Seminars in liver disease, 1992; 12:279-286.
28. Malik, IA., Ahmed, N., Luqman, M. et al. Hepatitis C as a case ofchronic liver disease in Northern Pakistan. J. Pak. Med. Asaoc., 1992;42:67-68.
29. Mc-Mahon, A. The histological features of asymptomatic hepatitis C virus Antibody positive blood donors. Histopathology, 1994;24:517-524.