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Study concerning the histopathological changes in chronic hepatopathies

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Abstract

Chronic liver diseases represent a public health problem both at global level and in our country. Their significance is due not only to the large number of cases but also to their severe complications and associated diseases, which increase the gravity of prognosis. Hepatopathies generally develop by formation and accumulation of fibrous tissue, which leads to architectural distortions in the structure of the liver. Hepatic fibrosis is the result of chronic injury and plays a direct role in the pathogenesis of the hepatocellular dysfunction and portal hypertension. Histopathological changes depend on the stage of the disease and are an essential factor in the therapeutic options and prognosis of the disease. The analysis of histopathological changes at the level of the liver, in the patients with chronic liver disease evaluated by this study, shows that mesenchymal lesions and dystrophy have been present in more than 90% of the subjects, parenchymal lesions in 85% of the cases and fibrosis in 50% of the patients. In relation to the types of disorders, in chronic hepatitis the most frequent lesions described have been portal inflammation, portal fibrosis, and inflammatory infiltrate. In liver cirrhosis portal inflammation, porto-portal fibrosis and biliary neocanaliculi are also prevalent. The results of this study demonstrate the fact that, with the evolution of the disease, histopathological changes are more numerous and more pronounced.

Keywords: chronic liver disease, pathological changes, parenchymal lesions, fibrosis, dystrophy.

Introduction

Liver diseases represent an important part of all digestive diseases, affecting approximately 12% of the population in our country [1]. Chronic liver disease is one of the most important death causes worldwidely, representing about 1.03 million deaths every year [2, 3]. Morbidity associated with chronic hepatopathies has increased in the last 30 years, this trend being due to more and more efficient and nuanced diagnosis possibilities, to a decrease in the age of patients at the moment of diagnosing the liver disease and the increased cost of some treatments, which requires an exact diagnosis of the hepatic pathology, in order to appropriately choose the persons that might benefit from such an expensive treatment.

In the etiopathogeny of chronic liver disease, there interfere a series of toxic factors (like excessive alcohol intake, as the most incriminated one), viral factors (post-viral chronic hepatitis), non-alcoholic hepatic steatosis, autoimmune hepatitis, etc. [4, 5].

In this context it is necessary to emphasize the presence of a relationship between histopathological changes in the liver and the different types and stages of chronic hepatopathies.

Aim

The main purpose of this study is to analyze the histopathological changes in the liver of patients with chronic hepatopathies, chronic hepatitis and liver cirrhosis, in relation to the stage of the disease.

Patients, Materials and Methods

Liver puncture biopsy (LPB) became an essential method for diagnosing and staging primitive liver diseases, for setting the therapeutic conduct and for evaluating therapeutic response. Echo-guided puncture biopsy has been performed in 281 patients, hospitalized within the Department of Clinical Gastroenterology, Emergency County Hospital of Oradea, Romania, between October 2011 and October 2014. The tissue material obtained was fixed in 8% formalin solution, immediately after biopsy. Processing was performed in paraffin blocks, cut at 4 μm with the microtone, the sections being stained with Hematoxylin–Eosin (HE), in order to better highlight inflammatory activity, and with Goldner–Szekely (GS) trichrome, in order to assess liver fibrosis. Only histo-pathological fragments, including at least six portal fields, were taken into consideration (for this reason two patients initially selected for the study were excluded, as their biopsy specimens showed less than six portal fields).

Statistical analysis

The statistical processing of data was performed with the help of the MedCalc statistical software, version 11.4.3.0, based on the information initially collected in Excel, version 2007.

Results

The major percent of the study sample was represented by the male population (67.41%); about 77.66% of the

subjects were older than 50 years, the average age being older in female subjects, as compared to the situation of male subjects (57.75 years old/56.33 years old). Subjects living in urban areas prevailed (57.18%). In terms of etiology types, 225 (80.07%) patients had chronic hepatitis and 56 (19.93%) patients had cirrhosis.

Mesenchymal lesions

The histopathological examination revealed mesenchymal lesions in 262 patients, of whom 214 (81.68%) patients had chronic hepatitis and 48 (18.32%) had cirrhosis. The most frequent mesenchymal lesions were portal inflammation (89.69%) and portal fibrosis (64.12%). Portal inflammation (90.65%) and portal fibrosis (72.89%) were more frequently found in patients with chronic hepatitis, while portal inflammation (85.41%) was more common in hepatic cirrhosis (Figure 1).

Porto-portal fibrosis has been identified in 19.84% of all the patients. Portal fibrosis was significantly more frequent in patients with chronic hepatitis, as compared to those suffering from liver cirrhosis ($p<0.02$), while porto-portal fibrosis was significantly more frequent in patients with liver cirrhosis as compared to those with chronic hepatitis ($p<0.001$). Biliary neocanaliculi and hyperplasia of biliary canaliculi have been revealed in 11.63% of the subjects, while in terms of etiologies, more frequent and statistically significant ($p<0.001$) they were in subjects with liver cirrhosis (33.33%) as compared to subjects with chronic hepatitis (7%). In less than 5% of the subjects, some other mesenchymal lesions could be described: biliary stasis, blood stasis and ductopenia.

Parenchymal lesions

Parenchymal lesions were seen in 241 (85.76%) patients, of whom 197 (81.74%) patients had chronic hepatitis and 44 (18.26%) patients had liver cirrhosis. More than 83% of the patients with parenchymal lesions showed inflammatory infiltrate of the intralobular type (202 patients, 83.81%), while centrolobular aspect was present in 27 (11.20%) patients. In 113 (46.89%) patients, the inflammatory infiltrate had a nodular aspect. In chronic hepatitis, the inflammatory infiltrate was present in 32 (16.24%) patients, necrosis in 49 (24.87%) patients and infiltrate and necrosis in 116 (58.88%) patients. In liver cirrhoses, the inflammatory infiltrate was present in 16 (36.36%) patients, necrosis in 10 (22.72%) patients and infiltrate and necrosis in 18 (40.90%) patients (Figure 2).

The most frequent necroses were the focal ones (176 cases, 73.02%), followed by the periportal (piecemeal) necroses in 82 (34.02%) cases. Periportal and bridging necrosis was present in 36 (14.93%) patients (Figures 3 and 4).

Focal necrosis was present in high proportions in both diagnosis groups (74.11% in chronic hepatitis, respectively 68.18% in liver cirrhosis), while periportal (piecemeal) necrosis was identified significantly more frequently in liver cirrhosis (43.18%), as compared to chronic hepatitis (31.97%) ($p<0.04$). Instead, periportal and bridging necrosis was more frequent in chronic hepatitis (15.73%) as compared to liver cirrhosis (11.36%) (Figure 5).

Inflammatory infiltrate was present in 49 (20.33%) subjects, necrosis in 61 (25.31%) patients, while the simultaneous presence of inflammatory infiltrate and of necrosis was noted in 131 (54.36%) cases. In terms of etiology types, the inflammatory infiltrate was identified in 36.36% of the patients with liver cirrhosis, two times more frequently than in patients with chronic hepatitis (16.24%) ($p<0.001$). Necrosis was present in 24.87% of the cases with chronic hepatitis, while in those with liver cirrhosis it was identified in 22.72% of the cases. In both etiologies, the infiltrate + necrosis prevailed, this being more frequent in chronic hepatitis (58.88%), as compared to liver cirrhosis (40.91%) (Figure 6).

Fibrosis

Fibrosis was present in 148 (52.66%) patients. The most frequently encountered type of fibrosis was the porto-central (band) fibrosis in 112 (75.67%) patients, followed by the intralobular one in 44 (29.72%) cases. Cetrilobular fibrosis was present in 15 patients, representing 10.13% of all patients with fibrosis. In terms of etiology types, fibrosis was encountered in 107 (47.55%) patients with chronic hepatitis and in 41 (73.21%) patients with liver cirrhosis, the difference being statistically significant ($p<0.05$). Porto-central (bands) fibrosis was predominant both in chronic hepatitis (72.89%) and in liver cirrhosis (82.92%), followed by intralobular fibrosis (28.97% in chronic hepatitis and 31.7% in liver cirrhosis). Centrilobular fibrosis was less frequent, presenting insignificant statistical differences in the cases of chronic hepatitis (9.34%) and liver cirrhosis (12.19%) (Figure 7).

Dystrophy

Dystrophy was present in 256 (91.1%) cases. In relation to dystrophy types, the following have been registered in patients with chronic hepatopathies:

- granular dystrophy in 171 (66.79%) patients;
- microvacuolar fat dystrophy in 146 (57.03%) patients;
- macrovacuolar fat dystrophy in 138 (53.9%) patients;
- hydropic dystrophy in 102 (39.84%) patients.

Dystrophy was present in 208 (92.44%) patients with chronic hepatitis and in 45 (80.35%) patients with liver cirrhosis, the difference being insignificant ($p>0.05$).

Fat dystrophy (microvacuolar and macrovacuolar) was identified in a higher percentage in liver cirrhosis as compared to chronic hepatitis, while granular and hydropic dystrophies were prevalent in chronic hepatitis (Figure 8). Both in chronic hepatitis and in liver cirrhosis, granular dystrophy and fat dystrophy were present in a percentage of over 50%, while hydropic dystrophy was present in approximately 40% of the patients, in both diagnosis groups. The differences recorded were not statistically significant ($p>0.05$) (Figure 9).

Table 1 presents other histopathological changes identified in the patients evaluated by our study. Hyperplasia and proliferation of Kupffer cells were identified in a total of 103 (36.65%) patients, of whom 85 (37.77%) patients were with chronic hepatitis and 18 (32.14%) patients had liver cirrhosis. The distorted architecture of hepatocytes was recorded in 41 (14.59%) patients, of whom 15 (6.66%) were with chronic hepatitis and 26 (46.42%) with liver cirrhosis, the difference being significant as compared to chronic hepatitis ($p<0.001$).

Table 1 – *Other changes identified on histopathological examination*

Histopathological examination	Total (281 cases)		Chronic hepatitis (225 cases)		Liver cirrhosis (56 cases)	
Other histopathological changes	***No.***	***%***	***No.***	***%***	***No.***	***%***
Hyperplasia and proliferation of Kupffer cells	103	36.65	85	37.77	18	32.14
Distorted architecture of hepatocytes	41	14.59	15	6.66	26	46.42
Dilated sinusoids	27	9.6	26	11.55	1	1.78
Glassy liver nuclei	23	8.18	21	9.33	2	3.57
Nuclear inequalities	18	6.4	16	7.11	2	3.57
Disorganization of lobular architecture	14	4.98	3	1.33	11	19.64
Infiltrate in sinusoids	12	4.27	10	4.44	2	3.57
Bile pigment in cytoplasm	1	0.35	1	0.44	0	0

In chronic hepatitis, dilated sinusoids were identified in 11.55% of the patients, glassy hepatic nuclei in 9.33% of the subjects and nuclear inequalities in 7.11% of the patients, differences which are significantly higher than in liver cirrhosis (p<0.001). The rest of histological changes are found in less than 5% of the patients. The significant difference (p<0.001), given by the identification in liver cirrhosis of disorganized lobular architecture in 19.64% of the patients, as compared to 1.33% of the patients with chronic hepatitis, is noteworthy.

Metavir score

Metavir score was determined in all the 281 patients undergoing histological examination. Lesions described histopathologically are presented in the following way: activity (A) includes periportal necrosis and lobular necrosis, while fibrosis (F) is marked separately. Histopathological lesions are presented horizontally, while the intensity of lesions was presented on the vertical plane, through a semiquantitative evaluation, from A0 to A3 for activity, and from F0 to F4 for fibrosis (Table 2).

As indicated by the Metavir score, parcelar and lobular necrosis was absent in four (1.43%) cases; it was minimal in 110 (39.14%) patients, moderate in 139 (49.46%) patients and severe in 28 patients. Fibrosis was absent in 14 (4.98%) cases; portal, stellate, without septa was present in 101 (35.94%) patients, and with septa in 73 (25.98%) patients. Many septa without cirrhosis were found in 37 (13.17%) patients and with cirrhosis in 56 (19.92%) patients (Figure 10).

Table 2 – *Metavir score*

Score	Activity		Fibrosis	
	No.	***%***	***No.***	***%***
0	4	1.43	14	4.98
1	110	39.14	101	35.94
2	139	49.46	73	25.98
3	28	9.96	37	13.17
4	–	–	56	19.92

According to the Metavir score, intralobular necrosis was absent in only three (1.33%) cases with chronic hepatitis and in one patient (1.78%) with liver cirrhosis (Table 3; Figure 11).

Table 3 – *Metavir score in chronic hepatitis and liver cirrhosis*

Score	Chronic hepatitis (225 cases)				Liver cirrhosis (56 cases)			
	Activity		***Fibrosis***		***Activity***		***Fibrosis***	
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
0	3	1.33	14	6.22	1	1.78	–	–
1	104	46.22	101	44.88	6	10.71	–	–
2	98	43.55	73	32.44	41	73.21	–	–
3	19	8.44	37	16.45	9	16.07	–	–
4	–	–	–	–	–	–	56	100

In chronic hepatitis, parcelar and lobular necrosis were minimal or moderate (46.22% and 43.55%), and fibrosis was stellate without septa in 44.88% of the cases and with septa in 32.44% of the patients (Figure 12).

In liver cirrhosis, the majority of cases (73.21%) had moderate parcelar and lobular necrosis, and grade 4 fibrosis was obviously present in all patients.

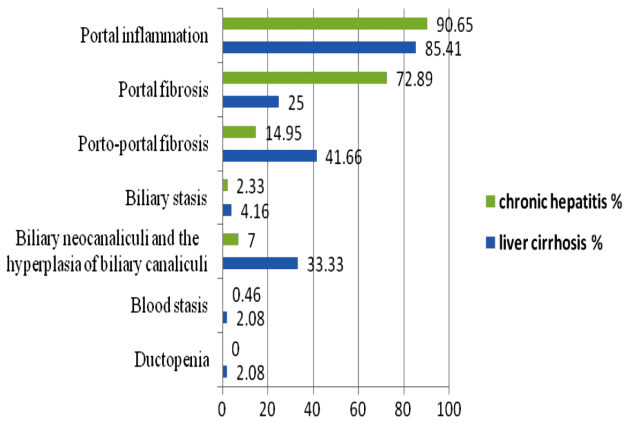

Figure 1 – *Histopathological examination: mesenchymal lesions in chronic hepatitis and liver cirrhosis.*

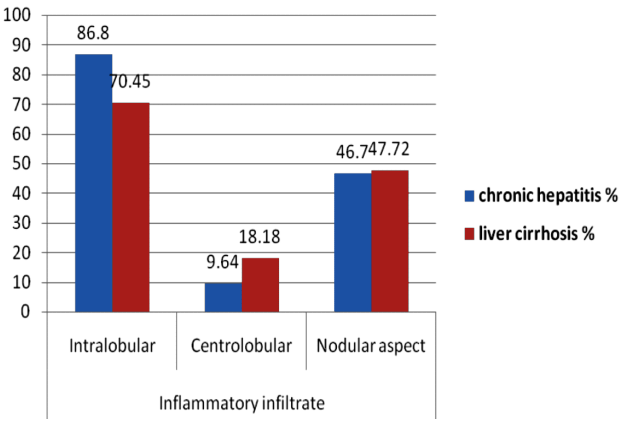

Figure 2 – *The aspect of the inflammatory infiltrate in terms of etiology type.*

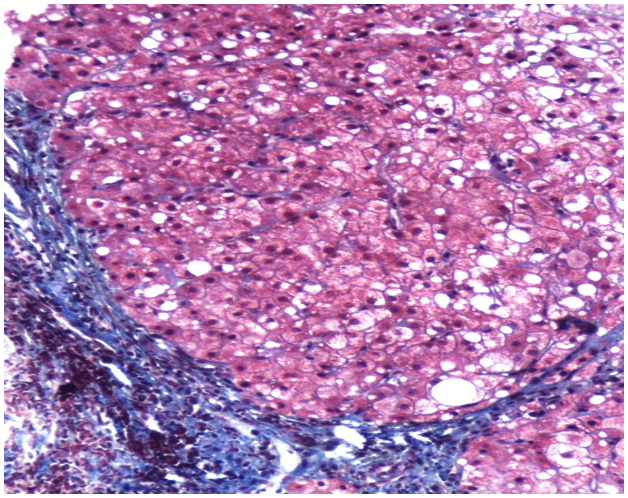

Figure 3 – ***Liver cirrhosis with porto-portal bridges and the tendency to form cirrhotic nodules (GS trichrome staining, ×200).***

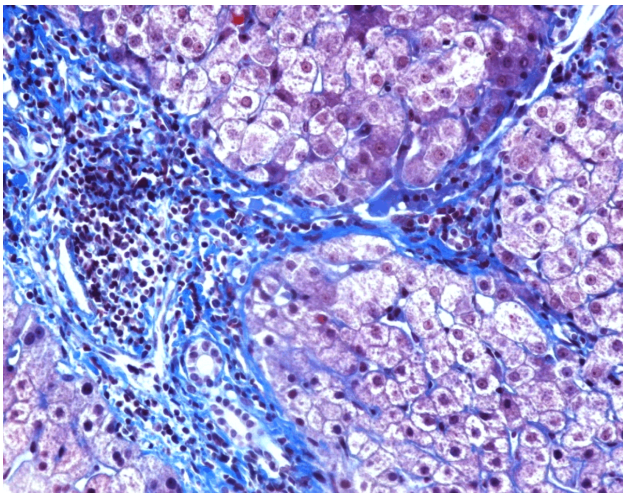

Figure 4 – ***Liver cirrhosis, porto-portal bridges, and inflammatory infiltration in Kiernan space (GS trichrome staining, ×200).***

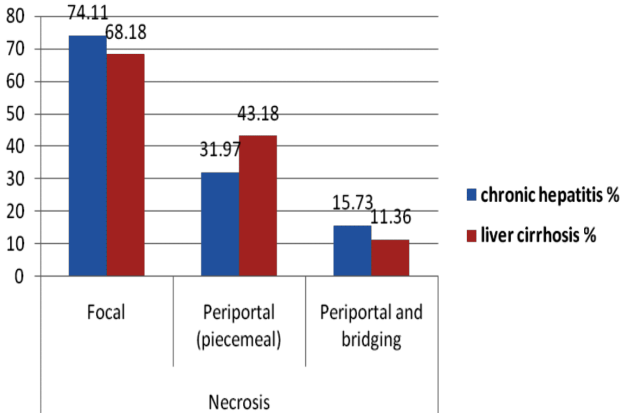

Figure 5 – ***Types of necrosis in chronic hepatitis and liver cirrhosis.***

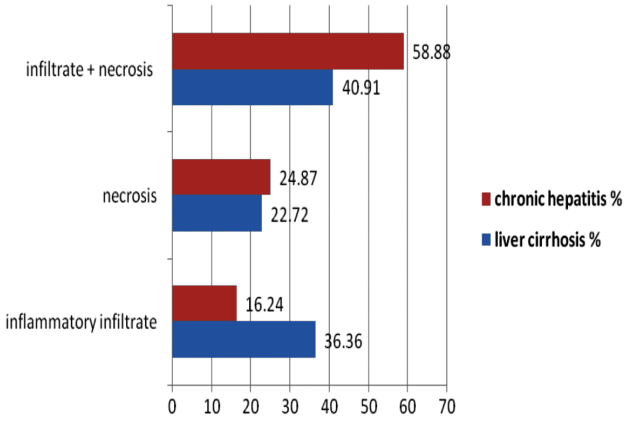

Figure 6 – ***Parenchymal lesions of the inflammatory infiltrate and necrosis in chronic hepatitis and liver cirrhosis.***

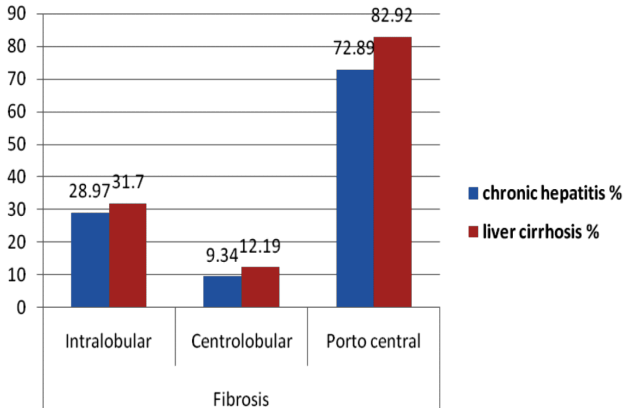

Figure 7 – ***Types of fibrosis in chronic hepatitis and liver cirrhosis.***

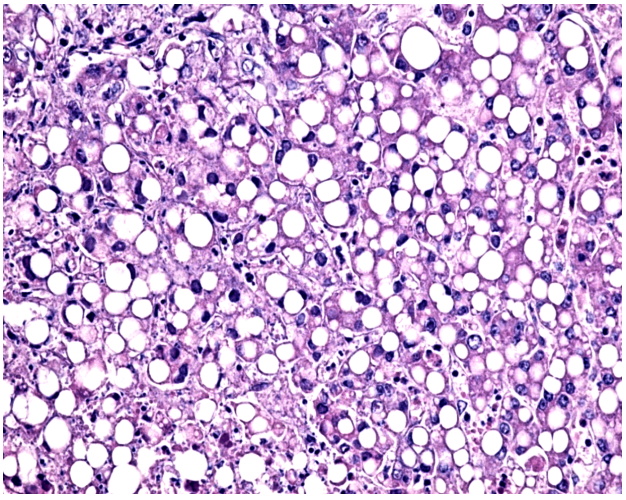

Figure 8 – ***Image of liver with intense macrovascular dystrophy (HE staining, ×200).***

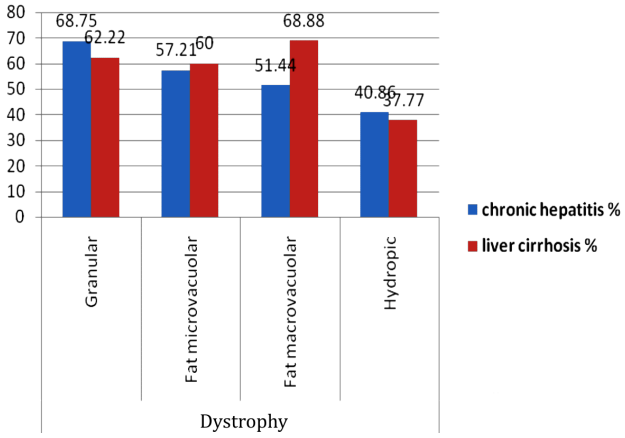

Figure 9 – *Dystrophy types recorded in chronic hepatitis and liver cirrhosis.*

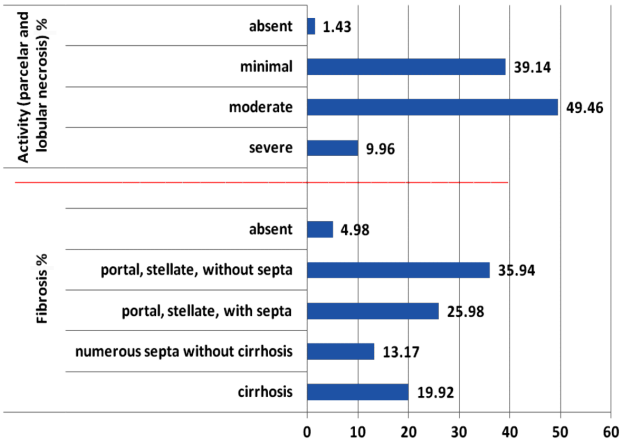

Figure 10 – *Histopathological lesions. Metavir score.*

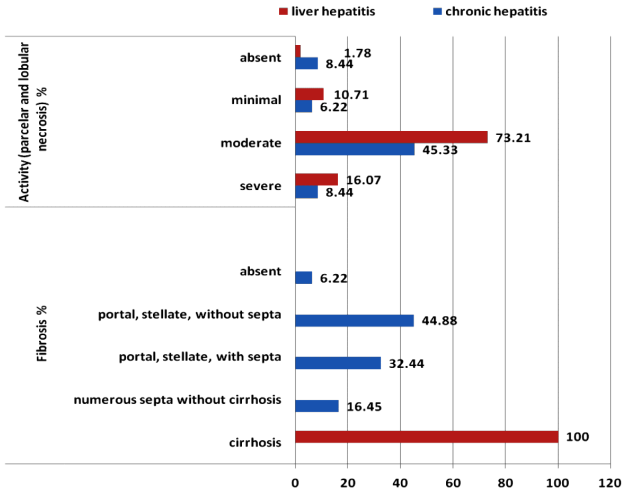

Figure 11 – *Metavir score in chronic hepatitis and liver cirrhosis.*

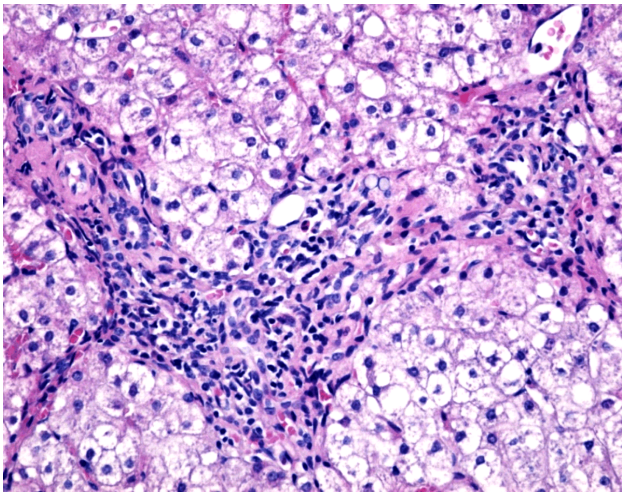

Figure 12 – *Liver with active chronic hepatitis (HE staining, ×400).*

Discussion

In the initial stage, the cases studied histopathologically were analyzed altogether, the lesions present in chronic hepatopathies being investigated and centralized, and then the analysis was performed on groups of diseases, chronic hepatitis and liver cirrhosis. The overall analysis showed that all patients presented histopathological changes. The most frequent mesenchymal lesions were portal inflammation (in almost 90% of the patients) and portal fibrosis (64.12%). The remaining lesions were present in less than 20% of the patients: porto-portal fibrosis, bile stasis, biliary neocanaliculi, blood stasis and ductopenia. These lesions are described in similar percentages in literature [6–8].

Liver fibrosis appears as a response reaction to the chronic liver aggression, independent of the aggression etiology [9–11].

Liver fibrosis is the result of the synthesis and excess deposit of extracellular matrix, extremely rich in collagen I and III, elaborated by fibroblasts and myofibroblasts present in the liver [12–14]. In its turn, liver fibrosis initiates a cascade of biochemical and morphological events in the liver microenvironment, causing necrosis and apoptosis of hepatocytes and sinusoid endothelial cells, activation of stellate liver cells and stimulation of inflammatory cells for the synthesis and release of high quantities of inflammatory mediators and profibrosis cytokines [15].

Between the liver inflammatory process and fibrillogenesis, there is a very close relation. Most studies show that chronic inflammation, present in most chronic liver diseases (postviral hepatitis, toxic hepatitis, alcoholic hepatitis, non-alcoholic steatohepatitis, autoimmune diseases of the liver) is the main cause of liver fibrogenesis [16, 17]. Inflammatory cells release a multitude of cytokines, chemokines and reactive oxygen species that stimulate the transformation of perisinusoidal dendritic cells in myofibroblasts, these producing high quantities of conjunctive matrix rich in collagen. According to certain opinions, perisinusoidal dendritic cells represent the main effective cells responsible for the onset of liver fibrosis [18, 19]. Untreated liver fibrosis will evolve and cause liver cirrhosis, portal high blood pressure, organ failure and even death [20, 21].

In our study, the most frequent parenchymal lesions were the intralobular inflammatory infiltrate (83.81%) and focal necrosis (73.02%). Inflammatory infiltrate with nodular aspect was present in 46.88% of the patients, while centrilobular inflammatory infiltrate, piecemeal necrosis and bridging necrosis were present in less than 25% of the cases. Porto-central fibrosis was present in 75.67% of the cases, and granular dystrophy was recorded

in 66.79% of the patients. These lesions, described in our group of patients, are not different from the pathological changes described in literature [22–24].

The calculation of Metavir score indicated the fact that the most common activity was of the moderate type (49.46%), followed by the minimal one (39.14%), while the most frequent fibrosis was of the portal type, without septa (35.94%), followed by the portal one, with septa (25.98%). Our results proved to be similar to those obtained by Scheuer & Lefkowitch [25] and Geller & Petrovic [26], who described the most important pathological changes associated with chronic hepatopathies.

By types of diseases, comparing the group of patients with chronic hepatitis and the group of subjects with chronic cirrhosis, one could identify both similarities and differences in relation to the existing literature. Data consistent with information presented in literature [27–29] were obtained in relation to mesenchymal lesions, where portal inflammation was present in high percentage (more than 85%) in both types of diseases, portal fibrosis being more frequent in chronic hepatitis (72.89%) and porto-portal fibrosis (41.66%) and biliary neocanaliculi (33.33%) being more frequent in liver cirrhosis. Parenchymal lesions described correspond to data in literature [30–33], where, in both types of diseases, the intralobular inflammatory infiltrate, with nodular aspect, predominates – in a proportion higher than 95% for the inflammatory infiltrate in chronic hepatitis. Dystrophy does not present significant different percentages in the two types of disease.

Conclusions

The histological techniques used demonstrated that mesenchymal lesions and dystrophy were present in more than 90% of the patients, parenchymal lesions in 85% of the patients, and fibrosis in 50% of the patients. In relation to lesion types, portal inflammation (89.69%) and portal fibrosis (64.12%), intralobular inflammatory infiltrate (83.81%) and focal necrosis (73.02%), porto-central fibrosis (75.67%) and granular dystrophy (66.79%) predominated. In terms of etiology types, more frequent and significant statistical differences were found in chronic hepatitis as compared to liver cirrhosis for: portal fibrosis (p<0.02), dilated sinusoids, glassy liver nuclei and nuclear inequalities (p<0.001); and more frequent differences in liver cirrhosis as compared to chronic hepatitis for: porto-portal fibrosis (p<0.001), bile neocanaliculi and biliary canaliculi hyperplasia (p<0.001), periportal (piecemeal) necrosis (p<0.04), inflammatory infiltrate (p<0.001), fibrosis (p<0.05), distorted architecture of hepatocytes (p<0.001), disorganization of lobular architecture (p<0.001). The most frequent activity was of the moderate type (49.46%), followed by the minimal one (39.14%), and the most frequent fibrosis was of the portal type, without septa (35.94%), followed by portal fibrosis with septa (25.98%). The histopathological study in chronic hepatopathies demonstrates the fact that, with the evolution of the disease, histopathological changes become more numerous and more accentuated.

Conflict of interests

The authors declare that they have no conflict of interests.

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