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Histopathological aspects described in patients with chronic hepatitis C

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Abstract

Chronic hepatitis C affects an estimated 170 million people worldwide and causes approximately 350 000 deaths each year. The current antiviral therapy allows the virus eradication or the permanent inhibition of the virus replication (sustained virological response, SVR), the reduction of the inflammation, and the prevention or the reduction of liver fibrogenesis (histological response). We studied the histopathological aspects found during percutaneous liver biopsy in patients with chronic hepatitis C viral infection who were treated and monitored over a period of two years. The assessment of the histological activity index through Ishak score determined the presence of: mild chronic hepatitis in 12 (23.1%) patients, moderate chronic hepatitis in 21 (40.4%) patients, and severe chronic hepatitis in 19 (36.5%) patients. The percutaneous liver biopsy performed on the patients with chronic viral hepatitis C showed a series of histological alterations, the most frequent being: portal inflammation, periportal necrosis, lobular inflammation, focal necrosis, and hepatic fibrosis (scarring). The severity degree of this histopathological aspect was correlated with the hepatitis activity index. The association of piecemeal with bridging necrosis is the deadline at which the antiviral treatment can still be effective. Evidence of early fibrosis represent the important moment for the antiviral treatment start. The specific histopathological aspects, but not pathognomonic, of chronic hepatitis C (hepatic steatosis, portal lymphoid infiltrates and bile duct damage) had a reduced incidence, occurring in only half (hepatic steatosis), a quarter (portal lymphoid infiltrates) and a fifth (destruction of biliary ducts) of all the patients with chronic viral hepatitis C, and these patterns was correlated with advanced degree of necroinflammatory process of the liver, particularly in the portal tracts.

Keywords: chronic hepatitis, portal inflammation, lymphoid infiltrates, liver biopsy, hepatic steatosis.

Introduction

Chronic viral hepatitis C affects over 170 million people worldwide and it is a major cause of morbidity and mortality, these patients being exposed to a high risk of developing hepatic cirrhosis, liver insufficiency and hepatocellular carcinoma [1, 2].

The current antiviral treatment allows the cure of over 75% of the patients with chronic hepatitis C virus infection [3]. The main goal of the therapy is the virus eradication or the permanent inhibition of the virus replication (sustained virological response, SVR) from all body compartments (serum, liver, and mononuclear cells) [4]. Secondary goals are the reduction of the inflammation and the prevention or the reduction of liver fibrogenesis (histological response), accomplished through aminotransferases normal values and improvement of the histological aspect [5]. Therefore, the histological response represents an important aspect to monitor during antiviral treatment [6].

The aim of this study was to establish the opportunity of the antiviral treatment in accordance with histopathological aspects described in patients with chronic hepatitis C.

Patients and Methods

We carried out a retrospective clinical trial in which the histopathological aspects found during liver biopsy on 52 patients with chronic hepatitis C were analyzed, the patients were monitored and treated with antiviral medication over a period of two years in the IInd Medical Clinic, Emergency County Hospital of Craiova, Romania.

The chronic hepatitis C diagnosis was suggested by the clinical examination, backed-up by the serum tests (anti-HVC antibody screening), and confirmed by liver biopsy and virological tests (quantitative HCV RNA test). The selection criteria for including the patients in the study group were the following: age range from 18 to 70 years; the presence of anti-HCV antibodies; detected viral load HCV RNA; normal values of hematological (platelet count >150 000/mm^3) and biochemical parameters (prothrombin index >70%). The criteria for leaving out the patients from on the study group were: clinical and paraclinical signs of cirrhosis (hemorrhagipar syndrome, edema, bleeding esophageal varices, ascites); autoimmune diseases (autoimmune hepatitis, autoimmune thyroiditis, collagenosis); psychic disorders (chronic alcohol abuse,

high-risk drug addiction and hepatotoxic drugs) and non-cooperative patients.

The liver biopsy was performed on the patients from the study group through percutaneous method, using the special kit Hepafix® (B. Braun Melsungen AG, Germany). The liver tissue samples removed (with dimensions between 10–25/1–1.4 mm) were placed in formaldehyde and then analyzed according to the standard protocol performed in the Laboratory of Pathological Anatomy, Emergency County Hospital of Craiova.

Results

We studied the histopathological aspects found during percutaneous liver biopsy in patients with chronic viral hepatitis C infection who were treated and monitored over a period of two years.

The patients group consisted of 12 men and 40 women, with ages raging from 18 to 70 years, with body weights varying from 55 to 120 kg.

The clinical manifestations described by patients were: asthenia (40 patients; 76.9%), digestive manifestations (24 patients; 46.1%), arthralgia and arthritis (15 patients; 28.8%), neuropsychiatric manifestations (13 patients; 25%), hemorrhagic manifestations (eight patients; 15.3%) and vascular purpura (seven patients; 13.4%). The main clinical signs detected in these patients were: hepatomegaly (42 patients; 80.7%), splenomegaly (20 patients; 38.4%) and jaundice (four patients; 8%).

The ultrasound examination showed values of antero-posterior diameter of the left lobe raging between 6.2 and 9.3 cm, with an average value of 7.35±0.74 cm. The dimensions of the left lobe were over 6.7 cm (hepato-megaly) in 42 (80.7%) patients. The homogenous aspect of the liver occurred in 32 (62.15%) patients, while the inhomogeneous aspect found in 20 (37.85%) patients. Liver steatosis with diffuse inhomogeneous aspect occurred in 21 (40.38%) patients, while multifocal nodular steatosis was recorded in only two (3.8%) patients. The longitudinal diameter of the spleen had values raging from 9 to 14.2 cm, with an average value of 11.7±1.74 cm. The longitudinal diameter of the spleen over 12 cm (splenomegaly) was recorded in only 24 (46.1%) patients. The diameter of hepatic portal vein, measured in the hepatic hilum, had values raging from 0.7 to 1.4 cm, with an average value of 1.1±0.19 cm. The value of the portal vein diameter over 1.3 cm (ultrasound sign of portal hypertension) was larger in only four (7.6%) patients.

The hematological values recorded in these patients had the following averages: hemoglobin 13.2±2.98 g% (9.1–16.6 g%), leukocyte count 6535.5±2184.88/mm^3 (3130–9530/mm^3), and platelet count 215 143.25±93 857.08/mm^3 (90 000–366 000/mm^3).

The biochemical parameters assessed for the patients with chronic hepatitis had the following average values: total bilirubin 1.16±0.4 mg% (0.8–2.2 mg%), alanine aminotransferase (ALT) 107.8±67.5 U/L (21–258 U/L), aspartate aminotransferase (AST) 96.64±47.82 U/L (24–300 U/L), albumin 3.73±0.54 mg% (3.1–4.5 mg%), prothrombin index 92.9±7.4% (79–100%).

The average value of HCV RNA titer recorded for the patients with chronic hepatitis was 1 040 477.05± 497 842.96 copies/mL, with limits from 807 to 3 510 000 copies/mL (Table 1).

The assessment of the histological activity index (HAI) through Ishak score determined the presence of mild chronic hepatitis (HAI 1–8) in 12 (23.1%) patients, moderate chronic hepatitis (HAI 9–12) in 21 (40.4%) patients, and severe chronic hepatitis (HAI 13–18) in 19 (36.5%) patients (Table 2).

Table 1 – ***Hematological, biochemical, and virological characteristics in patients with chronic hepatitis C***

	Mild chronic hepatitis (12 pts; 23.1%)	**Moderate chronic hepatitis (21 pts; 40.4%)**	**Severe chronic hepatitis (19 pts; 36.5%)**
Hemoglobin [g%]	13.26±2.1	12.93±3.67	13.42±3.18
Leukocyte count [/mm^3]	7438.33±2091.21	6504.76±2195.24	5668.42±2268.21
Platelet count [/mm^3]	270 525±95 475	199 904.76±118 096.24	175 000±68 000
Total bilirubin [mg%]	1.1±0.3	1.2±0.5	1.2±0.4
ALT [U/L]	77.62±35.3	121.04±88.96	124.74±78.26
AST [U/L]	65.6±32.4	114.66±45.54	109.68±65.53
Albumin [mg%]	3.9±0.5	3.8±0.54	3.5±0.58
Prothrombin index [%]	94.5±6.4	93.8±6.3	90.4±9.6
ARN–VHC titer [copies/mL]	827 376.08±342 589.67	1 026 476.19±535 489.81	1 267 578.94±615 449.41

Table 2 – ***Ishak score which determined the severity of the necroinflammatory lesions and of liver fibrosis based on the samples taken through liver biopsy punction***

Necroinflammatory activity								**Fibrosis**	
Periportal or periseptal interface hepatitis (piecemeal necrosis)	***Score***	***Confluent necrosis***	***Score***	***Focal (spotty) lytic necrosis, apoptosis and focal inflammation***	***Score***	***Portal inflammation***	***Score***	***Description***	***Score***
Absent	0	Absent	0	Absent	0	Absent	0	No fibrosis	0
Mild (focal, few portal areas)	1	Focal confluent necrosis	1	One focus or less per ×10 objective	1	Mild, some or all portal areas	1	Fibrous expansion of some portal areas, with or without short fibrous septa	1
Mild (focal, few portal areas)	2	Zone 3 necrosis in some areas	2	Two to four foci per ×10 objective	2	Moderate, some or all portal areas	2	Fibrous expansion of most portal areas, with or without short fibrous septa	2

Necroinflammatory activity								Fibrosis	
Periportal or periseptal interface hepatitis (piecemeal necrosis)	***Score***	***Confluent necrosis***	***Score***	***Focal (spotty) lytic necrosis, apoptosis and focal inflammation***	***Score***	***Portal inflammation***	***Score***	***Description***	***Score***
Moderate (continuous around <50% of tracts or septa)	3	Zone 3 necrosis in most areas	3	Five to 10 foci per ×10 objective	3	Moderate / marked, all portal areas	3	Fibrous expansion of most portal areas, with occasional portal to portal bridging	3
Severe (continuous around >50% of tracts or septa)	4	Zone 3 necrosis + occasional portal-central (P-C) bridging	4	More than 10 foci per ×10 objective	4	Marked, all portal areas	4	Fibrous expansion of most portal areas, with marked bridging (portal to portal as well as portal to central)	4
		Zone 3 necrosis + multiple P-C bridging	5					Marked bridging with occasional nodules (incomplete cirrhosis)	5
		Panacinar or multiacinar necrosis	6					Cirrhosis, probable or definite	6

The histopathological changes determined more frequently in patients with mild chronic hepatitis were portal inflammation in 14 (100%) patients, with an average score 1, focal necrosis in 14 (100%) patients, with an average score of 1.16±0.32, piece-meal necrosis in 14 (100%) patients, with an average score 1 and lobular confluent necrosis in only five (41.6%) patients, with an average score of 0.41±0.04. Other morphopathological aspects determined seldom in these patients were lymphoid infiltrates in three (25%) patients (Figure 1), microvesicular and macrovesicular steatosis in two (16.6%) patients and lesions of the biliary ducts in one patient (8.33%). Liver fibrosis occurred in 11 (91.66%) patients, with an average score of 1.25±0.65. Stage 0 of fibrosis occurred in one patient only (8.33%), stage 1 in seven (58.33%) patients, and stage 2 in four (33.3%) patients.

The histopathological aspects determined in patients with moderate chronic hepatitis were portal inflammation in 21 (100%) patients (Figure 2), with an average score of 1.72±1.28, focal necrosis in 21 (100%) patients, with an average score of 1.8±1.2, piece-meal necrosis in 21 (100%) patients, with an average score of 2.57±0.43, and lobular confluent necrosis in 12 (57.1%) patients, with an average score of 0.85±0.61. The morphopathological aspects described seldom in these patients were lymphoid infiltrates in 12 (57%) patients, microvesicular and macrovesicular steatosis in eight (38.09%) patients and bile ducts damages in four (19.04%) patients. Liver fibrosis found in these patients was determined for all 21 (100%) patients, with an average score of 1.76±0.24. Stage 2 of fibrosis was present in 18 (85.71%) patients and stage 3 in three (14.29%) patients.

The histopathological alterations determined in patients with severe chronic hepatitis were portal inflammation in 19 (100%) patients (Figure 3), with an average score of 2.52±0.5, focal necrosis in 19 (100%) patients (Figure 4), with an average score of 2.84±1.46, piece-meal necrosis in 19 (100%) patients, with an average score of 3.1±0.75 and lobular confluent necrosis in only 15 (78.9%) patients, with an average score of 1.42±0.87. Liver fibrosis described in the patients with severe chronic hepatitis was determined in all 19 (100%) patients (Figure 5), with an average score of 3.57±1.48. Stage 2 of fibrosis occurred in one patient (5.2%) only, stage 3 occurred in nine (47.36%) patients, stage 4 in seven (36.84%) patients, stage 5 in one patient (5.2%), and stage 6 in one patient (5.2%).

Other morphopathological aspects determined seldom in these patients were lymphoid infiltrates in nine (47.36%) patients, microvesicular and macrovesicular steatosis in seven (36.84%) patients (Figure 6) and bile duct damage in five (26.31%) patients.

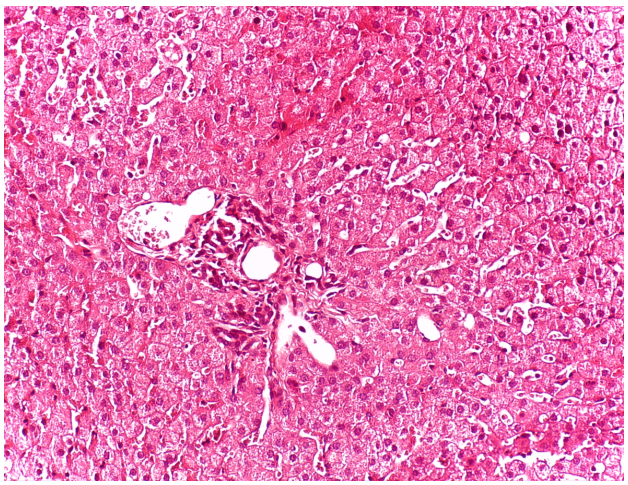

Figure 1 – ***Histological aspect of chronic viral hepatitis C (CVHC) with mild activity. HE staining, ×100.***

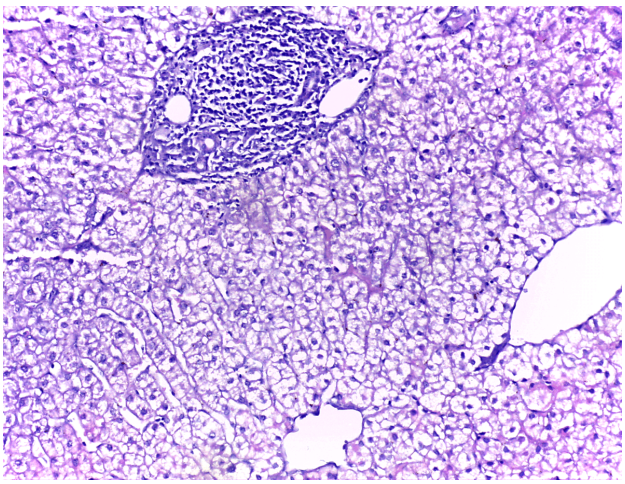

Figure 2 – ***Histological aspect of CVHC with moderate activity. HE staining, ×200.***

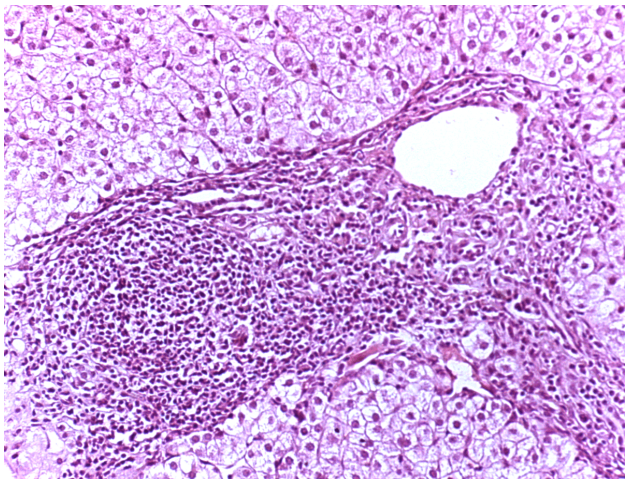

Figure 3 – ***Histological aspect of CVHC with severe activity. Portal inflammation with an inflammatory infiltrate consisting of lymphocytes, plasmocytes and polymorphonuclears inside the portal tracts. HE staining, ×200.***

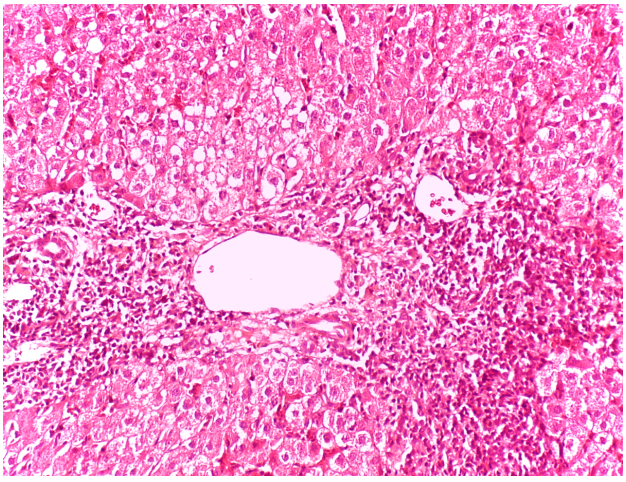

Figure 4 – ***Section of the liver biopsy specimen of patient with CVHC. Focal necrosis with non-specific histopathological alterations, located at intralobular hepatocytes level. HE staining, ×200.***

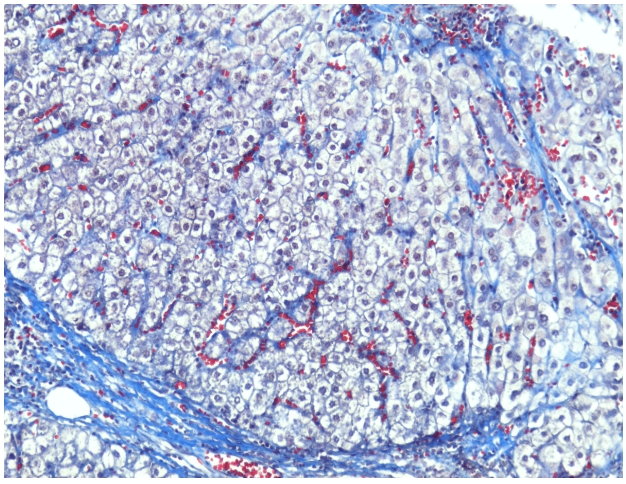

Figure 5 – ***Microscopic image of CVHC associated with porto-portal and porto-central fibrosis. GS trichromic staining, ×200.***

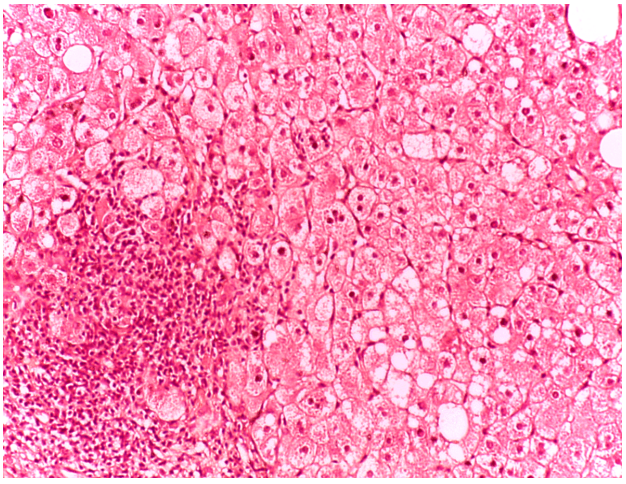

Figure 6 – ***Section of the liver biopsy specimen of patient with CVHC. Hepatic steatosis, with many vesicles in the cytoplasm of hepatocytes with net limits of various sizes. HE staining, ×200.***

Discussion

The most frequent histopathological aspects described in patients with chronic viral hepatitis C were the portal inflammation, periportal necrosis (piece-meal necrosis), focal necrosis and liver fibrosis [8]. The histopathological changes found seldom in these patients were confluent necrosis (bridging necrosis), hepatic steatosis, lymphoid infiltrates and lesions of the biliary ducts [9].

Portal inflammation, found in all patients (52 patients; 100%) with chronic viral hepatitis C, was the result of the presence of an inflammatory infiltrate inside the portal tracts consisting of lymphocytes, plasmocytes and polymorphonuclears [10, 11]. The severity degree of the inflammation was in direct relation to the chronic hepatitis activity, thus the average severity degree of inflammation was one in mild chronic hepatitis, 1.72 in moderate chronic hepatitis, and 2.52 in severe chronic hepatitis. The presence of portal inflammation in all patients with chronic hepatitis C who had had biopsy makes this histological marker useless as a marker for antiviral therapy starting point [12].

Periportal necrosis, as a histological marker of necro-inflammatory activity of chronic viral hepatitis C was determined in all selected patients (52 patients; 100%), and it defines the necrosis of periportal lobular hepatocytes, due to the intralobular spreading of inflammatory infiltrate in the portal space. Periportal hepatocytes showed a series of alterations, such as: ballooning degeneration, acidophilic cytoplasm, apoptosis, as well as pseudo-glandular pattern of hepatocytes (rosette formation). Piece-meal necrosis had different degrees of severity in accordance with the hepatitis activity index: average degree 1 in mild chronic hepatitis, average degree 2.57 in moderate chronic hepatitis and average degree 3.1 in severe chronic hepatitis. The spreading and distribution of periportal necrosis were uneven, so that in mild and moderate forms of hepatitis there were isolated focal spots of piecemeal necrosis, while in severe forms the periportal necrosis affected the entire area of portal spaces [13]. Furthermore, in severe forms, apart from the necrosis alterations and hepatocyte inflammation, the emergence of portal fibrosis septa was observed, which marked out an aggravation of

chronic viral hepatitis C and implicitly the necessity of antiviral treatment initiation [14].

Focal necrosis of intralobular hepatocytes is characterized by non-specific histopathological alterations, similar to those found in acute hepatitis, located at intralobular hepatocytes level [15]. It occurred in all selected patients (52 patients; 100%) and it had different degrees of severity in accordance with the hepatitis activity index: average severity degree of 1.1 in mild chronic hepatitis, average degree of 1.8 in moderate chronic hepatitis, and average severity degree 2.8 in severe chronic hepatitis. The spreading of focal necrosis varied in accordance with the activity level of chronic hepatitis, thus in mild hepatitis, the focal necrosis was limited, while in severe hepatitis focal necrosis was associated with confluent necrosis [16].

Confluent necrosis represents the extended necrosis of intralobular hepatocytes, in the form of necrosis areas that join the portal spaces between themselves (porto-portal necrosis) or the portal spaces with the lobular vein (porto-central necrosis) [17]. Confluent necrosis (bridging necrosis) occurred in only 32 patients (61.5%; 32/52). The severity degree of confluent necrosis had different values in accordance with the hepatitis activity level; the values determined being 0.40 in mild chronic hepatitis, 0.88 in moderate chronic hepatitis and 1.42 in severe chronic hepatitis. We observed that the porto-portal necrosis occurred mostly in moderate hepatitis, while porto-central necrosis occurred in severe chronic hepatitis C. The occurrence of bridging necrosis explained the disorder rapid evolution, which was confirmed by the increased serum values of aminotransferases [18]. Moreover, the occurrence of confluent necrosis was correlate with the occurrence of intralobular fibrous septa (fibrotic bridging), implying the chronic hepatitis aggravation [19]. Therefore, we can say that the occurrence moment of bridging necrosis represent the appropriate moment for the antiviral treatment initiation, because the confluent necrosis fosters the moderate and severe fibrosis evolution, resulting in the occurrence of liver cirrhosis occurrence [20].

Hepatic fibrosis, recognized as the most important factor in deciding the moment for the initiation of antiviral treatment, [21] was diagnosed in the majority of patients with chronic viral active hepatitis C (98%; 51/52). It occurred in stage 0 in one patient (1.9%), in stage 1 in seven (13.7%) patients, stage 2 in 23 (45%) patients, stage 3 in 12 (23.5%) patients, stage 4 in seven (13.7%) patients, stage 5 in one patient (1.9%) and stage 6 in one patient (1.9%). The severity degree of fibrosis was correlated with the hepatitis activity index, the average degree of fibrosis being 1.25 in patients with mild chronic hepatitis; 1.76 in patients with moderate chronic hepatitis and 3.57 in patients with severe chronic hepatitis. If the stage 0 of fibrosis occurred in one patient (with mild chronic hepatitis), portal fibrosis occurred in 30 patients, portal and intralobular fibrosis in 19 patients, and liver cirrhosis in two patients (with severe chronic hepatitis). Therefore, evidence of early fibrosis (scarring) represent the important moment for the antiviral treatment initiation [22].

In addition to the diffuse portal inflammation, in 24 (46.1%) patients portal lymphoid infiltrates also occurred (located changes of portal inflammation). The distribution of this histopathological aspect was the following: 25% (3/12 patients) of the patients with mild chronic hepatitis, 57% (12/21 patients) of the patients with moderate chronic hepatitis, and 47.36% (9/19 patients) of the patients with severe chronic hepatitis.

Hepatic steatosis is characterized by lipid accumulation in hepatocytes, and is associated with portal and periportal activity more intense and advanced fibrosis [23, 24]. Vesicles in the cytoplasm of hepatocytes is affected optically empty due to dissolution of lipids during inclusion in paraffin, with net limits of various sizes. Hepatic steatosis can be micro- and macrovesicular [25, 26]. In micro-vesicular steatosis, we can notice small vesicles located around the nucleus. Macrovesicular steatosis is the most common, and appears through progressive accumulation of lipids, so the nucleus is pushed to the periphery. Sometimes, the two types of steatosis can coexist [27]. Hepatic steatosis occurred in 17 (32.6%) patients, the incidence of this alteration varying in accordance with the hepatitis activity index: 16.6% of the patients with mild chronic hepatitis, 38% of the patients with moderate chronic hepatitis and 36.8% of the patients with severe chronic hepatitis.

The destruction of the bile ducts was the histopathological aspect most rarely found in the patients with chronic hepatitis C (19.2%; 10/52), the incidence of this alteration depending on the hepatitis activity index: 8.3% in patients with mild chronic hepatitis, 19.04% in patients with moderate chronic hepatitis, and 26.31% in patients with severe chronic hepatitis. In optic microscopy, bile duct damage occurs as a parenchymal cholestasis, accompanied by hepatocyte resetting [28]. We can observe a defect in epithelial wall, the presence of vacuolation and stratification of epithelial cells, and the presence of lymphocytic inflammatory infiltrate [29]. Sometimes was described ductopenia. The occurrence of hepatitic bile duct injuries was correlated with advanced degree of necroinflammatory processes of the liver, particularly in the portal tracts. Frequently, γ-GT (gamma-glutamyl transpeptidase) was the parameter related to the presence of bile duct lesions [30].

Conclusions

The percutaneous liver biopsy performed on the patients with chronic viral hepatitis C showed a series of histological alterations, the most frequent being: portal inflammation, periportal necrosis, lobular inflammation, focal necrosis, and hepatic fibrosis (scarring). The severity degree of this histopathological aspect was correlated with the hepatitis activity index. The association of piecemeal with bridging necrosis is the deadline at which the antiviral treatment can still be effective. Evidence of early fibrosis represent the important moment for the antiviral treatment start. The specific histopathological aspects (but not pathognomonic) of chronic hepatitis C (hepatic steatosis, portal lymphoid infiltrates and bile duct damage) had a reduced incidence, occurring in only half (hepatic steatosis), a quarter (portal lymphoid infiltrates) and a fifth (destruction of biliary ducts) of all the patients with chronic viral hepatitis C, and these patterns were corre-

lated with advanced degree of necroinflammatory process of the liver, particularly in the portal tracts.

Conflict of interests

The authors declare that they have no conflict of interests.

Author contribution

All authors have contributed equally to the present work.

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