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Endothelial Markers and Fibrosis in Alcoholic Hepatitis

Roxana Popescu¹, Doina Verdes², Nicoleta Filimon³,
Marioara Cornianu⁴ and Despina Maria Bordean⁵

^{1,2,4}*University of Medicine and Pharmacy, Timisoara*

³*West University of Timisoara*

⁵*BUASVM Timisoara
Romania*

1. Introduction

The alcohol, consumed in great quantities and for a long period of time determines, directly or by its metabolites, serious alterations of the hepatic function and structure. The causal mechanisms underlying this disease are not fully understood. Histological features of chronic alcoholic hepatitis include: hepatocellular injury, inflammation and repair of the damage with activation of Kupffer cells and hepatocellular regeneration.

The hepatic extracellular matrix (ECM) plays an important role in the stability of tissues and in regulating the growth and differentiation of cells. Liver fibrogenesis occurs by disrupting the balance between ECM compounds degradation and production, especially the synthesis and deposition of collagen (Wang et al., 2000). The ECM is made up of conjunctive - vascular structures which ensure the functional and nutritional support of the parenchyma. Liver injury like hepatitis and cirrhosis, caused by alcohol, initiates response from hepatic stellate cell (HSC) that gets activated by oxidative stress resulting in large amounts of collagen. After an acute liver injury parenchymal cells regenerate and replace the death hepatocytes. The depositions of ECM structures are initially limited and are associated with an inflammatory response. If the hepatic injury persists and then the liver regeneration fails, the hepatocytes are substituted with abundant fibrillar collagen (Bataller & Brenner, 2005).

The expression of endothelial cells markers CD31 and CD34 is heterogeneous, with a specific pattern for individual vessel types and different anatomic compartments of the same organ (Pusztaszeri et al., 2006).

CD31 is a transmembrane glycoprotein, member of the immunoglobulin superfamily, also designated as PECAM-1 (platelet endothelial cell adhesion molecule 1). CD31 is expressed on the surface of circulating platelets, monocytes, neutrophils and selected T cell subsets, but, with a few minor exceptions, PECAM-1 is not present on fibroblasts, epithelium, muscle, or other nonvascular cells. PECAM is a major constituent of the endothelial cell intercellular junction and a key participant in the adhesion cascade leading to transmigration of leukocytes during the inflammatory process (Newman, 1997). Also,

several studies suggest that CD31 plays a major role in angiogenesis (DeLisser et al., 1997; Matsumura et al., 1997; Zhou et al., 1999).

CD34 is a 110-kDa transmembrane glycoprotein present on leukemic cells, endothelial cells and stem cells) (Pusztaszeri et al., 2006). CD34 is preferentially expressed on the surface of regenerating or migrating endothelial cells and is a marker of proliferating endothelial cells in the growing sprouts during angiogenesis (Poon et al., 2002). Usually, the liver sinusoids do not express CD34. But, pathological conditions can alter their phenotype and express this marker. Capillarization of hepatic sinusoids is a well-recognized phenomenon that occurs in long-standing liver disease and hepatic cirrhosis as well as in hepatocellular carcinoma (HCC) (Pusztaszeri et al., 2006).

The investigation of the expression of the endothelial cell markers CD31 and CD34 allow determining the degree of vascular distribution hepatic inflammation.

2. Histochemical and immunohistochemical diagnosis methods used for study of alcoholic hepatitis

2.1 Morphological diagnosis methods

The biological material harvesting by percutaneous liver biopsy or after a necropsy follows the same histological processing, involving fixing in formaldehyde 10%, inclusion in paraffin and making multiple serial sections. For routine diagnosis, deparaffinized sections from paraffin-embedded liver tissue were stained with hematoxylin-eosin technique (HE). For diagnostic purposes and to assess histopathological lesions, especially liver fibrosis, trichrome staining methods are applied in order to complement the data obtained on sections stained with HE. Gömöri method highlights collagen in green, on red background of hepatocytes cytoplasm. By Masson method, the results are similar; the color obtained for fibrosis is green-blue on a red background of the cytoplasm. The lumen of the centrilobular vein – collapsed or difficult to distinguish on HE staining – can be easily observed on reticulin silver staining, following the shape and wall thickness, the presence of inflammation or fibrosis. Silver impregnation by Gordon-Sweet method to highlight reticulin fibers (type III collagen) applied in all cases with histological activity and fibrosis, has proved useful in diagnosis of piecemeal necrosis indicating the outline of portal spaces altered by piecemeal necrosis, in evaluation of focal necrosis area and to highlight reticulin fibers in nodular regeneration conditions. The silver staining for reticulin highlight the components of extracellular liver matrix from Disse space and centrilobular venules (Cornianu et al., 2007).

2.2 Additional immunohistochemical diagnosis methods

Using immunohistochemical methods (IHC) as special techniques is a next step in diagnosis after histological staining, allowing highlighting of new structures and functions. In order to perform immunohistochemical reactions, the staining techniques based on monoclonal antibodies which react with specific tissue antigens are applied. The immunohistochemical detection is performed on 5-µm thick, routinely formalin-fixed, paraffin-embedded specimens. Briefly, the sections are deparaffinied in xylene and rehydrated in serial solutions of ethanol and water. To block endogenous peroxidase activity the sections are incubated in 3% hydrogen peroxide in PBS (phosphate buffered saline). Immunostaining are

performed with a monoclonal antibody diluted 1:50 in 1% bovine serum albumin in phosphate buffered saline. Antibody detection is usually performed using a horseradish peroxidase (HRP)-labeled goat anti-mouse secondary antibody followed by staining with a 3, 3'-diaminobenzidine chromogen (DAB) solution. Finally, slides are counterstained with hematoxylin. Positive staining is considered the cells with brown stain with a dotty, linear, semicircular or circular pattern.

3. Histopathological features in alcoholic chronic hepatitis

Alcohol hepatotoxicity is well known and generally related to the amount and duration of excessive consumption of alcohol. Alcoholic liver disease is characterized by a spectrum of clinical manifestations of liver, morphological modifications (Table 1)(Delladetsima et al., 1987; Kondili et al., 2005; Lefkowich, 2005; Lackner et al., 2008), as well associated injuries.

A. Alcoholic steatosis (fatty liver)
1. Macrovesicular steatosis
2. Microvesicular steatosis
3. Mixed variant of steatosis
4. Lipogranulomas
5. Foamy fatty degeneration
B. Alcoholic steatohepatitis
1. Ballooned hepatocytes (cell swelling)
2. Steatosis
3. Inflammation
4. Perivenular fibrosis
5. Vein occlusion
C. Cirrhosis
1. Micronodular cirrhosis that progress to macronodular cirrhosis
D. Hepatocellular carcinoma

Table 1. Morphological features in alcoholic liver chronic disease.

To establish the chronic character of liver disease three types of lesions proved to be definitive: portal inflammation, hepatocyte necrosis and fibrosis. For stabilization and determining the degree of chronic hepatitis can be taken in consideration other histopathological aspects: steatosis; lesions of biliary canaliculi which translates by swelling of biliary epithelial cells; intralobular degeneration lesions evidenced by presence of apoptotic bodies.

3.1 Steatosis

Alcoholic steatosis is the most common histopatological feature of chronic alcoholic liver disease, is the first manifestation of excessive alcohol consumption. In terms of histology is translated by the accumulation of lipid droplets in the form of vacuoles of various sizes in the cytoplasm. Hepatic steatosis is present under three forms: microvesicular,

macrovesicular and mixed. In microvacuolar form the lipid inclusions have small dimensions and they are evenly distributed in cytoplasm without changing the nucleus position while the macrovacuolar form is characterized by the presence of a single large vacuole, occupying the entire cytoplasm of the hepatocyte pushing the nucleus to the periphery. Although histologically can be traced all three forms, in most cases is present the macrovacuolar steatosis (Figure 1). Some authors use the term steatosis and steatohepatitis to designate the same lesion while alcohol can induce a pure steatosis without inflammatory components. At other patients alcohol induces an acute hepatitis superposed steatosis. Zonal distribution of steatosis in alcoholic liver disease involves initially zone three and then the acinar part of zone two following that in severe steatosis the distribution to be diffuse involving the entire acinus (Cornianu et al., 2007).

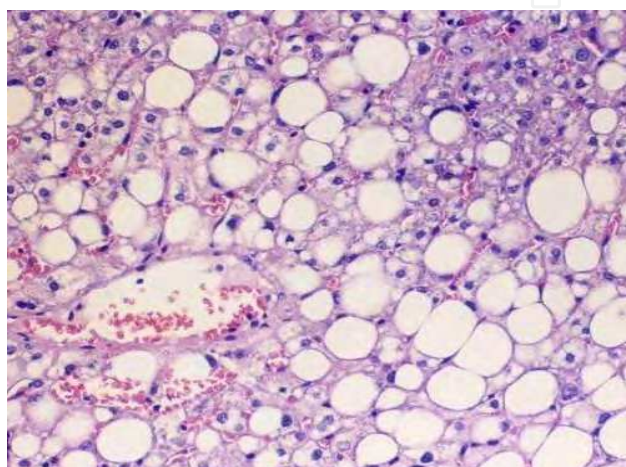


Fig. 1. Alcoholic chronic hepatitis, HE, x200 – panlobular macrovesicular steatosis with degenerative change.

3.2 Necroinflammatory process

The most important lesion in chronic hepatitis is “interface hepatitis” (piecemeal necrosis). Hepatocyte necrosis is with variable disposition and extension. It highlights coagulation necrosis of some isolated cells or Councilman acidophil bodies in periportal areas.

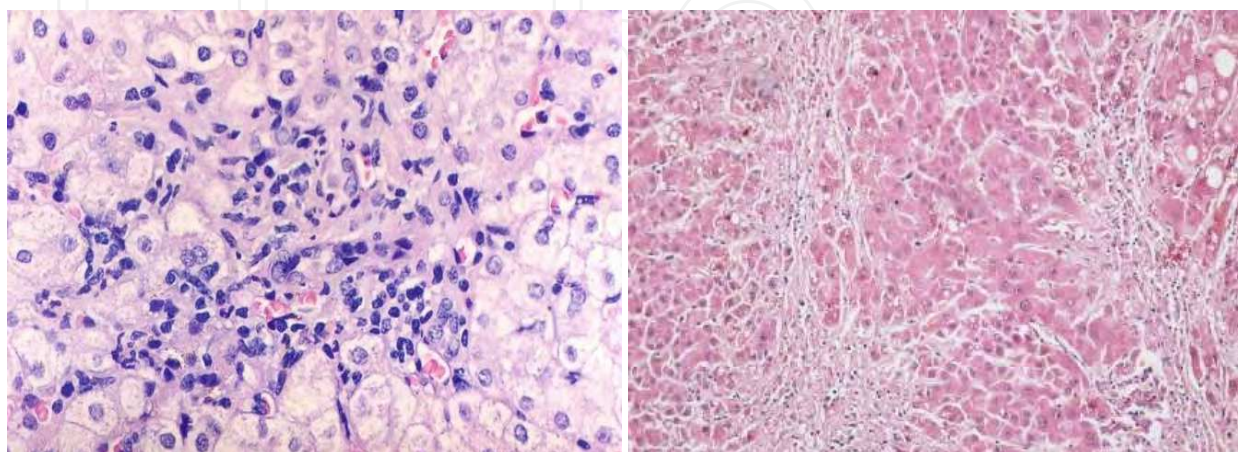


Fig. 2. Alcoholic chronic hepatitis. Focal necrosis, inflammatory infiltrate and acidophilic hepatocytes, HE, x200 (left). Bridging necrosis – large hepatocyte destruction (right).

Destruction of nearby group of hepatocytes located at the edge of liver parenchyma and portal connective structures, through cell-mediated immune mechanism, causes piecemeal necrosis. Unicellular necrosis located intralobular is betrayed by the presence of acidophil hepatocytes in an inflammatory outbreak. The infiltrative inflammatory process is made up of lymphocytes, plasmocytes but also of fibroblasts and fibrocytes (Figure 2). A more severe injury is confluent hepatic necrosis which forms porto-portal and porto-centrolobular bridges - bridging necrosis (Figure 2). Damaged hepatocytes place is taken by the collagen fibers and lymphocytes forming cords which linking the neighboring portal spaces and/or portal spaces and centrilobular veins. Association of periportal necrosis in bridges indicates a rapid progression to cirrhosis, in which the formed bridges become dense collagen septum which disorganizes the lobular architecture, forming hepatocyte nodules (Ishak, 2000).

3.3 Fibrosis

Fibrosis is an important element in chronic alcoholic hepatitis, being useful for the correct diagnosis, prognosis and the evolution of the disease. Toxic liver injury characterized by sinusoidal fibrosis, necrosis of pericentral hepatocytes, and narrowing and eventual fibrosis of central veins. The primary site of the toxic injury is represented by sinusoidal endothelial cells, followed by a circulatory compromise of centrilobular hepatocytes and fibrosis (De Leve et al., 2002). Liver cell necrosis is associated with varying degrees of perivenular, centrilobular, and pericellular fibrosis (Yip & Burt, 2006). Liver fibrosis is translated by a wide range of histopathological lesions:

- collagenization of the port areas (Figure 3)
- presence of bridging fibrosis porto-portal and porto-central fibrosis (as a consequence of disease progression) (Figure 3)
- perivenular fibrosis (Figure 4) (designated as a histological feature of alcoholic liver disease) – evidenced as a fibrous sleeve surrounding the terminal hepatic venula on at least two thirds of its circumference, being considered as a marker of progress to liver cirrhosis

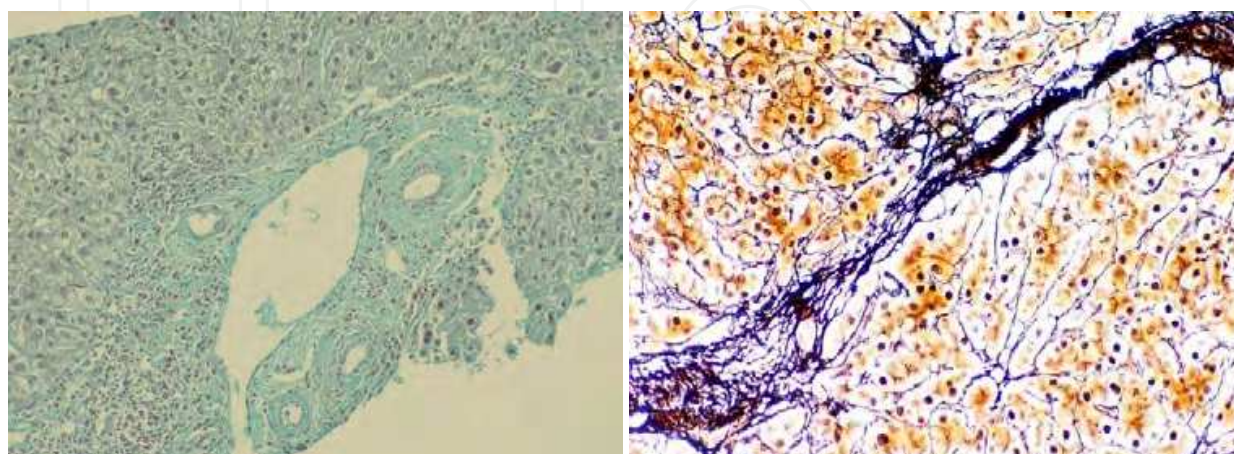


Fig. 3. Alcoholic chronic hepatitis. Portal fibrosis, Gömöri staining, x200 (left). Bridging fibrosis (porto-portal), silver staining, x200 (right).

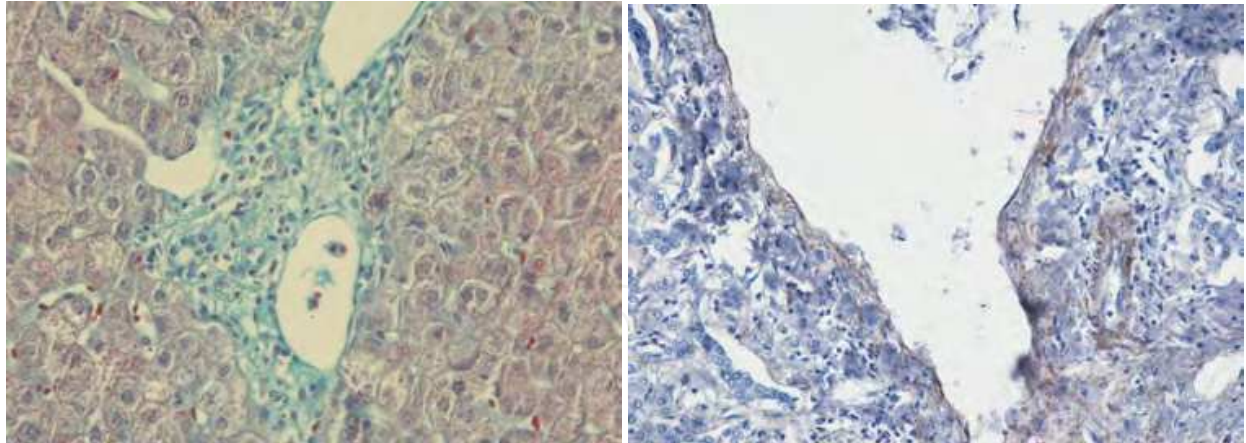


Fig. 4. Alcoholic chronic hepatitis – perivenular fibrosis. Gömöri staining, x400 (left) and Immunohistochemistry, collagen IV staining, x100 (right).

- collagenosis of the Disse space - capillarization of the hepatic sinusoids – accompanies progressive necroinflammation (Figure 5)
- regenerative nodules surrounded by fibrous connective septa (Figure 5)

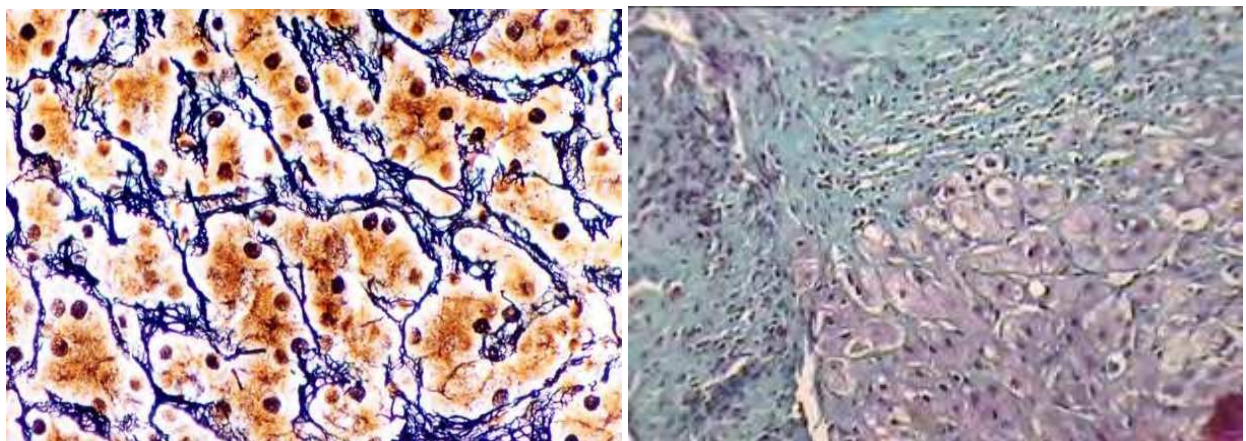


Fig. 5. Alcoholic hepatitis. Collagenization of the Diss space, silver staining, x400 (left) Fibrous connective septa, Gömöri staining, x400 (right).

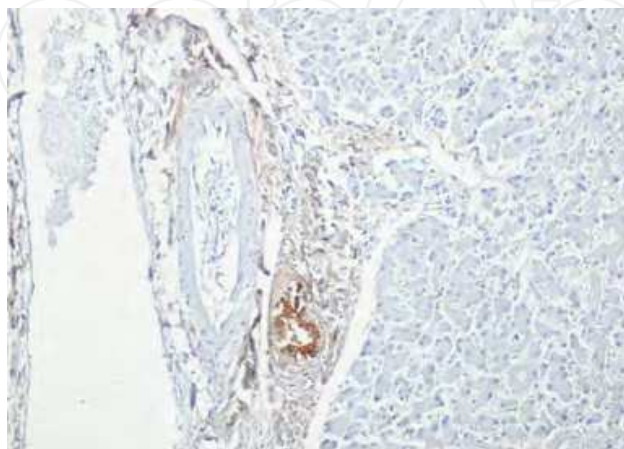


Fig. 6. Immunohistochemistry, collagen III positive staining at the portal area, x100.

In the fibrotic liver, the amounts of type III collagen (specific stroma) are increased not only in regions of portal fibrosis but also in the sinusoidal wall (Figure 6) (Sato et al., 2000). The first sign that the specific stroma participates in this liver injury is mirrored in the structure of the argyrophilic fibres. In the areas displaying of the hepatocytes necrosis, the process affects the argyrophilic fibres network of the specific stroma (Márcia Bersane et al., 2008). In an immunohistochemical study made on rat liver, Wei-Dong and collab., showed that in the normal liver, collagen I, III and IV is to be found at the level of the hepatic capsule, in the walls of blood vessels and in portal areas (Du et al., 1999). The hepatic sinusoids present positive reaction for collagen III and IV, but negative for collagen I (Marcia Bersane, 2008). Under pathological circumstances that engage the proliferation of the conjunctive tissue at hepatic level, numerous procollagen peptides-type IV and especially type III are formed in an excessive manner (Zhou et al., 2008). Collagen IV, being a constituent of the base membrane, accumulates in a precocious way both in viral hepatitis and in alcoholic hepatitis. Under conditions of viral or toxic aggression, collagen III and IV accumulates at the level of necrosis areas and along fibrous septa. In alcoholic hepatic fibrosis, increase the extracellular matrix protein expression of such as type III and IV collagen (Buck & Chojkier, 2003; Márcia Bersane, 2008; Bo et al., 2001; Fu et al., 2004). In the case of the alcoholic liver, in the fibroses areas, are detected an intensely positive reaction for collagen IV at the level of the portal tract and the central vein, but also at the level of Disse space, between the sinusoid cells and hepatocytes (Gorrellet al., 2003). After repeated injury, the extracellular matrix of basement membrane including type I, III, and IV collagen is over-deposited in perisinusoid (Li et al., 2005, Iwahashi et al., 2001).

4. Endothelial markers CD31 and CD34 expression and liver fibrosis

Under normal condition, the hepatic sinusoidal cells and the Kupffer cells express cell adhesion molecule like PECAM-1 (CD31) and ICAM-2 (intercellular cell adhesion molecule). Several studies were done to evaluate CD31 immunoreactions in liver disease, including alcoholic hepatitis. Ramadori et al. concluded that the expression pattern of CD31 is down regulated during inflammatory liver injury (Ramadori et al., 2008; Saile & Ramadori, 2007). In a study made on 103 patients with chronic viral and alcoholic hepatitis, Asanza remarked that the pattern of the CD31 expression is negative in lymphocytes, in the bile epithelium cells, in the hepatocytes in the periportal area and in the central lobular area, but positive in sinusoidal endothelial cells, as well as at the level of the lobular and portal vessels, both in mild affections of the liver and in severe hepatic inflammation (Asanza et al., 1997; Garcia et al., 1998). Similar results were also emphasized in other studies, suggesting at the same time, that CD31 plays an essential part in the transendothelium migration of the leucocytes, and in livers may facilitate adhesion and transmigration of inflammatory cells (Chosay et al., 1998; Lalor et al., 2002; Neubauer et al., 2008). Chosay and colleagues investigate the role of PECAM-1 in the pathophysiology of endotoxin-induced liver injury in a murine model. Their data showed that PECAM-1 is constitutively expressed on endothelial cells of large hepatic vessels, portal veins and arteries and hepatic veins, but not on sinusoidal endothelium (Chosay et al., 1998). The distribution of PECAM-1 in murine liver is similar to its distribution in human liver (Scoazec & Feldmann, 1991).

CD34 is preferentially expressed on the surface of regenerating or migrating endothelial cells and is a marker of proliferating endothelial cells in the growing sprouts during

angiogenesis (Schlingemann et al., 1990). Microvessels stained by anti-CD34 are capillary-like, rather than having the appearance of sinusoids in normal liver (Poon et al., 2002). In nontumor liver tissues CD34 expression was mainly confined to small vessels in the portal area and also seen in sinusoids in the liver parenchyma near portal areas, with dotted, linear, semicircular and circular staining patterns. In tumor tissues, the characteristics of positive staining were similar to those in nontumor tissues. A study made on 324 patients with chronic alcoholic hepatitis, proved that the pattern of expression CD34 was moderately expressed in the periportal endothelium cells (Chedidi et. al., 2004). Some researchers have proved that CD34 is expressed in chronic hepatitis at the level the progenitor oval cells (Paku, 2001; Forbes et al., 2002; Weiss et. al., 2008).

In our recent study, we investigated the expression of the endothelial cell markers CD31 and CD34 to determine the degree of vascular distribution in alcoholic chronic hepatitis and compare it with liver fibrosis. The immunohistochemical technique was made in order to complete the histological study and in order to highlight certain particular aspects of the liver when under aggression of toxic agents.

We noticed an unspecific lesion pattern, with variable histological aspects both at the level of the parenchyma and at the level of the extracellular matrix. At the lobular level we noticed areas with apparently unaltered architectonics but also some altered areas caused by the enlargement of the port spaces as a result of the inflammatory processes and/or fibrosis. At the port level, we signaled inflammation of varied intensity. The infiltrative inflammatory process is made up of lymphocytes, plasmocytes but also of fibroblasts and fibrocytes. The perilobular inflammatory process turns into an interlobular one on some preparations, the inflammatory infiltrate having the same structure as the one present at the level of the port area. The capacity of the immune system cells to infiltrate the liver represent a consequence of the hepatic toxic injury and has been characterized in alcoholic hepatitis. Leukocyte infiltration into the liver parenchyma of immune cells includes monocytes, lymphocytes and neutrophils (Thiele et. al., 2004). At the cell level, especially at the cells in the peripheral lobule area, thus in the proximity of the portal areas, we identified hepatocytes which displayed alterations of degenerative type: micro- and macro-vesicular steatosis and balloon cell degeneration (Le Bousse-Kerdilès et al., 2008).

By means of the trichromic colorations applied in all the study cases, we were able to identify the collagenization of the port areas, the collagenosis of the Disse spaces, perivenular fibrosis, and the extension of the fibrosis under the form of real fibrosis bridges. Through this the hepatic lesions were grouped in: minimum, mild, moderate and severe; while for fibrosis was obtained a valor scale from 1 to 4. Conform to fibrosis scoring methods the pathologic grading of fibrosis may be grouped in four categories (Table 2) (Brunt, 2000).

Score	Description
0	No fibrosis
1	Stellate enlargement of portal tract but without septa formation
2	Enlargement of portal tract with rare septa formation
3	Numerous septa without cirrhosis
4	Cirrhosis

Table 2. Fibrosis Scoring.

Histological examination revealed no fibrosis (F0) in 8 patients (19,51%), stage 1 fibrosis (F1) in 6 patients (14,6%), stage 2 (F2) in 12 patients (29,2%), stage 3 (F3) in 12 patients (29,2%) and stage 4 (F4) in 3 patients (7,3%)(Figure 7).

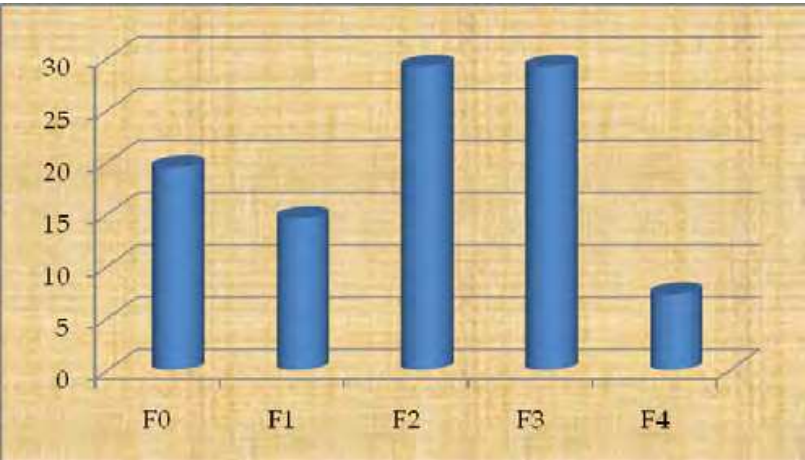


Fig. 7. The stage of fibrosis in patient with alcoholic liver disease.

In our study, all the cases with normal liver histology were CD31 and CD34 negative. By analyzing the immunohistochemical reaction for CD31 we have noticed that this one is negative for the central lobular area, but CD31-positive cells were observed in vessels of the portal area and in the sinusoids of the hepatic parenchyma near the portal area (Figure 8).

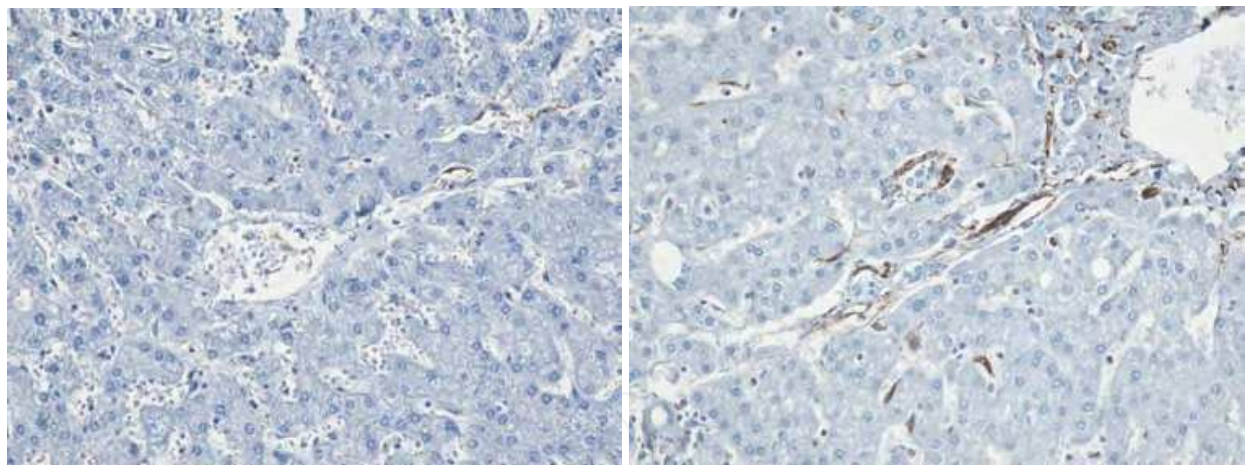


Fig. 8. Immunohistochemistry, anti CD31 staining, x100. Negative immunoexpression in central area (left) and positive expression in periportal space (right).

CD34 displays positive immunoreactions at the level of endothelium cells in the hepatic sinusoid in the periportal area, at the level of the central lobular vein as well as at the level of the venules and arterioles in the portal area (Figure 9) (Popescu et al., 2009).

CD34 positive reaction was found in 27,7% patients with F1 and F2 fibrosis and 73,3% patients with F3 and F4 fibrosis (Table 3). Additionally, the CD31 expression in all cases was mainly restricted to portal vessels and sinusoidal cells, in close relation with the periportal histological features or with inflammatory injury degree. CD31 pattern was positively expressed in 22,2% of cases with F1-F2 fibrosis and in 77,7% with F3-F4 of cases (Table 4).

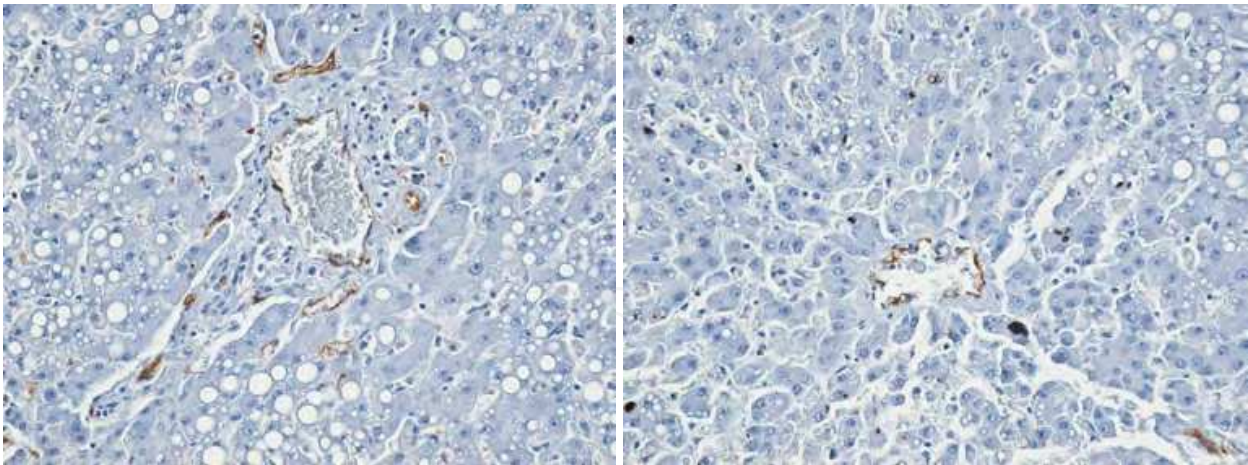


Fig. 9. Immunohistochemistry, anti CD34 staining, x100. CD34 expression in portal area (left) and central area (right).

CD 34	Stage F1 and F2	Stage F3 and F4
CD 34 positives cells	27.7%	73.3%

Table 3. Expression of CD34 in alcoholic liver.

CD 31	Stage F1 and F2	Stage F3 and F4
CD 31 positives cells	22.2%	77.7%

Table 4. Expression of CD31 in alcoholic liver.

Regarding correlation between stage of fibrosis and endolthelial cells markers, similar studies was done in liver disease. Akyol et al. investigate the relationships between the histopathological features of nonalcoholic fatty liver disease (NAFLD) and CD31 expression to identify hepatic stellate cell activation and capillarization. Their results showed a correlation between the fibrotic stage and CD31 expression, the highest staining scores of CD31 in zone 3, while the portal/septal area was the dominant zone for control groups (Akyol et al., 2005). On the other hand, angiogenesis plays an important role in chronic inflammation, accumulation of inflammatory infiltrate and fibrosis. In liver, angiogenesis is characterized by capillarization of the sinusoid. Also, Amarapurkar and colleague evaluate the expression of CD34, vascular endothelial growth factor (VEGF) and fibrosis in chronic liver disease (Amarapurkar et al., 2007). They report that none of patient with normal liver histology expressed the CD34 or VEGF positives cells. The capillarization and the histological change at the sinusoidal level occur with inflammation and fibrosis (Park et al., 1998). The degree of positivity increases with the stage of fibrosis. Also, they found significantly high expression of CD34 in hepatocellular carcinoma as compared to chronic disease. Increased vascular proliferation and pathological angiogenesis in hepatocellular carcinoma was reported in a comparison with chronic hepatitis and cirrhosis. The extracellular matrix affects the phenotype of the endothelial cells. The sinusoidal capillarization has the consequence the loss of endothelial fenestration and formation of variable amounts of basal membrane (Ichida et al., 1990; Semela & Dufour, 2004). Endothelial cells become positive for CD31 and CD34 and are used as indirect markers to detect microvascular density in liver carcinogenesis (Frachon et al., 2001).

5. Conclusion

To sum up, a direct correlation existed between endothelial cell markers CD31 and CD34 expression and the progression of fibrosis in alcoholic liver disease. The immunohistochemical methods of this molecule can be an important clue in future prognostic strategies.

6. References

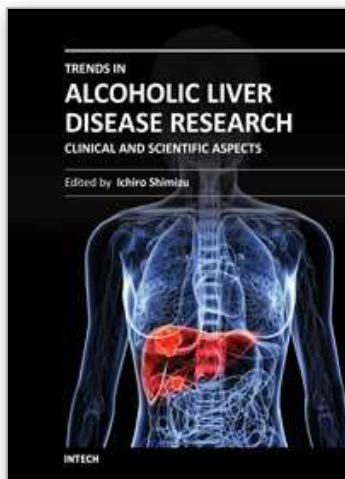
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Alcoholic liver disease occurs after prolonged heavy drinking. Not everyone who drinks alcohol in excess develops serious forms of alcoholic liver disease. It is likely that genetic factors determine this individual susceptibility, and a family history of chronic liver disease may indicate a higher risk. Other factors include being overweight and iron overload. This book presents state-of-the-art information summarizing the current understanding of a range of alcoholic liver diseases. It is hoped that the target readers - hepatologists, clinicians, researchers and academicians - will be afforded new ideas and exposed to subjects well beyond their own scientific disciplines. Additionally, students and those who wish to increase their knowledge will find this book a valuable source of information.

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University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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