Chronic Hepatitis C: Pathological Anatomy

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In infections with the hepatitis C virus (HCV), there is a wide spectrum of histological alterations that can affect the liver, from acute hepatitis to mild reactive phenomena to more severe forms, including chronic hepatitis with varying degrees of inflammation/fibrosis, cirrhosis, and hepatocellular carcinoma. In cases of acute hepatitis C, biopsies are rare, pathologists focusing their attention on the chronic form of the disease. The histological diagnosis of chronic hepatitis through liver biopsy remains extremely important in the management of patients infected with HCV, since it is the cornerstone of the detection of liver disease caused by the virus as well as the determination of the intensity of this disease. It should therefore be added to the diagnosis of infection made using serologic methods.

The basic parameter for the histological diagnosis of chronic hepatitis is the presence of portal inflammatory infiltrate, with predominance of lymphocytes, usually with variations in the number of plasmocytes and histiocytes. This inflammation is accompanied by periportal activity of varying degrees (also denominated interface activity or piecemeal necrosis), parenchymal activity (lobular) and fibrosis.

There are various classification systems using in the scoring and staging of chronic hepatitis [4,9,11,13,18,21,34]. Many of those systems are of historical importance. According to directive no. 863, issued by the São Paulo State Secretary of Health on November 4, 2002, it is recommended that one of two chronic hepatitis classification systems be used: the *Sociedade Brasileira de Patologia* (SBP, Brazilian Society of Pathology) system [13] or the METAVIR system [1,4]. These two systems are in fact very similar, and they both take into account the previously mentioned basic aspects of chronic hepatitis: periportal activity, lobular activity, and fibrosis. In addition to these, the classification system proposed by Ishak in 1995 [18] has been widely used in international literature. The Ishak system is an update of the system proposed by the same author in 1981, which gained popularity and was commonly referred to as the Knodell system [21] (a designation that should no longer be used), has been widely used in international literature. Table 1 shows an approximate correspondence between these systems, both for fibrosis (architectural alteration) and for periportal/lobular activity.

Protocol of Histological Evaluation for Liver Biopsies of Patients with Chronic viral Hepatitis

This protocol can be applied to several etiologies of chronic hepatitis, including, in addition to HCV, HBV, autoimmune hepatitis and, less frequently, Wilson's disease or some forms of drug-induced hepatitis. The protocol is based on the criteria of the SBP National Consensus of Chronic Hepatitis [13].

1) Sample type (needle biopsy, wedge biopsy, resected surgical sample, other):
2) Sample size
   Number of portal spaces in the biopsy: _____
3) Histological variables:

- Portal fibrosis:
  ( ) 0 (absent)
  ( ) 1 (discrete, without septum formation)
  ( ) 2 (with portal-portal septa)
  ( ) 3 (with portal-portal and portal-central septa, with formation of nodules – in 'nodular transformation')
  ( ) 4 (cirrhosis)
- Portal inflammation
  ( ) 0 (absent)
  ( ) 1 (discrete)
  ( ) 2 (moderate)
  ( ) 3 (pronounced)
  ( ) 4 (very pronounced)
- Periportal activity (interface activity)
  ( ) 0 (absent)
  ( ) 1 (presence of spillover only)
  ( ) 2 (discrete piecemeal necrosis – occasional foci in some portal spaces)
  ( ) 3 (moderate piecemeal necrosis – occasional foci in many portal spaces or innumerable foci in few portal spaces)
  ( ) 4 (pronounced piecemeal necrosis - innumerable foci in many portal spaces)
- Parenchymal activity
  ( ) 0 (absent)
  ( ) 1 (tumefaction, lymphocyte sinusoidal infiltrate and occasional foci of lytic hepatocytic necrosis)
  ( ) 2 (innumerable foci of lytic hepatocytic necrosis)
  ( ) 3 (occasional areas of confluent necrosis)
  ( ) 4 (innumerable areas of confluent necrosis or areas of panacinar necrosis)
- Histological evidence of association with other conditions:
  ( ) level _____ siderosis
  ( ) steatohepatitis markers
  ( ) others:_____

Nature and Size of the Liver Biopsy

Surgical biopsies performed with forceps generate subcapsular samples and should be discouraged, since the portal spaces in this location are frequently large, and it is

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Table 1. Approximate equivalence of the most widely used classification systems for the staging and scoring of chronic hepatitis

Architectural Alteration (Fibrosis)*		
SBP, 2000	**METAVIR, 1994**	**Ishak, 1995**
0	0	0
1	1	1 or 2
2	2	3
3	3	4 or 5
4	4	6

Inflammatory Activity**		
SBP, 2000 and Ishak, 1995		**METAVIR, 1994**
Parenchymal activity	**Periportal activity A**	
0 or 1	0	0
0 or 1	1 or 2	1
2	0–1	1
2	2	2
2	3–4	3
3	0–2	2
3	3–4	3
4	0–4	3

SBP= *Sociedade Brasileira de Patologia* (SBP, Brazilian Society of Pathology). *Maximum Ishak score, 6; maximum METAVIR score, 4; maximum SBP score, 4. **Corresponds to periportal and parenchymal activity, independently, for SBP and Ishak, and mixed periportal and lobular for METAVIR; in the METAVIR classification, the activity score reaches 3, whereas in Ishak and SBP it reaches 4.

difficult or impossible to correctly evaluate the presence of fibrosis. Even during the surgical procedure, therefore, liver biopsy should be performed with a needle. In addition, the biopsy should preferably be performed at the outset of the surgery in order to prevent alterations secondary to surgical manipulation.

Data in the literature demonstrate that the size of the needle biopsy greatly influences the result of the analysis [8,10,15,33,35]. Samples measuring 3.0 cm or more in length, show hepatitis with mild activity, as a result, in only 50% of the cases; 1.5-cm long samples, in 60%; and those measuring 1.0 cm or less, in almost 90% of the cases [8]. Other authors have also considered 1.5 cm as the minimum size for diagnosis in needle liver biopsy [35]. Thin needles have also provided inferior results [8,33]. Bedossa et al. [3] only achieved a precision plateau with 2.5-cm long biopsies. Therefore, 1.5-cm long biopsies should be considered the minimum necessary size and, ideally, they should measure 2.5 cm or more. Larger diameter needles, such as Tru-Cut needles, are also recommended.

Steatosis

Approximately 50% of the biopsy samples collected from patients with HCV present steatosis [17,40]. The evaluation of the presence of steatosis, its scoring, and the evaluation of the presence of associated steatohepatitis has gradually become more important [6,7,12,16,19,20,24,29-32,36,40].

The spectrum of steatosis, steatohepatitis and cirrhosis has been denominated nonalcoholic fatty liver disease (NAFLD). Although NAFLD is common in the population in general, concomitance between NAFLD and HCV is 2-3 times greater than what would be expected only at random [24]. In patients with chronic HCV infection, steatosis has been attributed to a series of factors usually associated with NAFLD, including high body mass index, insulin resistance and old age [16,26,31]. Evidence also indicates that steatosis contributes to the progression of fibrosis in a pattern similar to that seen in NAFLD [7,16,17,40].

It has been suggested that steatosis can also result from the viral cytopathic effect, especially in patients infected with genotype 3. In a series of patients with genotype 3 and steatosis, a sustained virological response led to regression of steatosis in 91% of the cases, a much higher index than the 19% observed for those who did not present sustained virological response [6], making the cytopathic effect a more consistent cause of steatosis. Other authors have reported similar results [22,36].

In HCV-positive patients, it is currently essential to characterize steatosis and related injuries, especially the presence and quantification of perisinusoidal and centrilobular fibrosis, which characterizes steatohepatitis. The lesson we learn from steatosis is that, in HCV-infected patients, biopsy is an instrument for the detection of liver diseases, whether associated with the virus or not, and that we should be prepared for other (probably less common) liver diseases that might be present in a particular case.

Histopathological Aspects of Post-Transplant HCV Recurrence

Immediate post-transplant virological recurrence of HCV is universal, and the progression of the disease is more rapid

than in non-transplanted patients [22A]. Long-term studies have shown that 70-90% of cases will present histological recurrence of the disease [20A,23A]. In most cases, hepatitis C histologically manifests in the same manner before the transplant: with portal and parenchymal inflammation, aggression of the interface with piecemeal necrosis, and fibrosis at portal spaces. Steatosis and ductal injury are also common findings. Earlier findings are often predominantly lobular, with inflammation and apoptotic bodies (acute hepatitis), and steatosis is occasionally the first histological manifestation [4A]. In a small proportion of cases, hepatitis C can result in a severe, rapidly progressive cholestatic pattern, which leads to loss of the graft [36A,41,42]. Due to the low tolerance of transplanted individuals to the treatment with interferon and ribavirin [24A,45], the evaluation of the biopsy is crucial for indication of treatment. Some anatomopathological aspects can be useful in predicting its evolution: histological recurrence in less than six months [46]; level of inflammatory activity [23A,44]; marked ballooning of hepatocytes; and cholestasis [43].

Histopathological Criteria for Possible Predictive Value of Worse Evolution

In chronic hepatitis, the contribution of the histopathological analysis of the samples collected by liver biopsy is currently considered decisive for diagnosis, for staging of the architectural damage, and for determining the level of necroinflammatory activity, assuming a decisive role in indicating the therapy with antiviral agents.

In our view, in addition to reports on that decision, as summarized in the METAVIR, Ishak, Scheuer, and Desmet classification systems, or, among us, the SBP/Brazilian Society of Hepatology consensus led by Gayotto, most recent evidence brings back the need of a detailed report of each of the principal forms of liver damage, and there have been studies that demonstrate a more rapid evolution of cases that present, among other predictive factors, more interface activity, confluent necrosis of hepatocytes, and steatosis [47,48].

A study involving 106 patients with initial biopsy presenting architectural staging 0 or 1 and re-biopsied after a mean interval of 7.8 years (minimum of 48 months) [48] revealed progression of architectural damage in 64 cases (60.4%), suggesting the need for therapeutic intervention, even in infected individuals not yet presenting significant alterations to the hepatic architecture. Among the predictive factors for progression of the injury, those authors highlight the level of necroinflammatory activity: 31.2% of the cases with moderate activity (A2) presented progression, which only occurred in 2.3% of those without activity (A0) and the presence of steatosis (progression in 87.5% of the cases with > 30% cells with steatosis, in 80% of those with < 30% steatosis, and in only 48.6% without steatosis).

Other authors also emphasize the presence and extent of steatosis as a risk factor for progression of injuries in chronic hepatitis C, either resulting from viral cytopathic effect, as proposed for genotype 3a [49], or associated with coexistent steatohepatitis, alcoholic [50] or nonalcoholic [47]. A recent meta-analysis including 3068 Italian patients infected with HCV and submitted to biopsy [51] confirmed that steatosis is independently associated with genotype 3, fibrosis, diabetes, inflammatory liver activity, drinking, body mass index, and older age.

Important experience was brought to debate in the most recent European Hepatology Congress: analyzing predictive factors of damage progression in 563 cases of HCV with mean intervals between biopsies of 5.4 years [52], it was determined that, in contrast to generic approaches that suggested that liver damage progress in a relatively uniform, linear manner, the speed of progression varied considerably in each patient. These authors, selecting statistically significant variables, identified the risk of progression associated with various architectural alterations (Table 2).We find, therefore, that important current studies demonstrate the outstanding contribution of histopathological findings in the discrimination of differentiated progression risk in patients chronically infected with HCV. More than dividing patients in classes that deserve antiviral treatment or not, most recent evidence point to the need of reviewing the systems of histological scoring, and the pathologist should inform, in addition to the stage of architectural alteration, the level of each type of necroinflammatory damage in each acinar compartment of the liver.

Table 2. Progression risks of architectural alterations

Factor	Relative Risk
Age > 50 years	1.6
Brindging necrosis	4.0
Confluent necrosis	3.4
Piecemeal necrosis	2.9
Steatosis	
Moderate/Pronounced	3.8
Discrete	2.1
Perivenular fibrosis	2.6

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