Histological scoring of chronic hepatitis

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Abstract

Liver biopsy is considered to be the most specific analysis to assess the nature and severity of liver disease. In case of chronic hepatitis, scoring liver biopsies is an established part of the pathologist's work. Four different scores are most often used : the Scheuer, Ludwig and French METAVIR systems, which are fairly simple, and the Ischak score, which is more complex. All systems generate scores, which are based upon inflammatory activity (the grade) and fibrosis (the stage), with splitting of these two components. To be valid in routine analyses, a scoring system must be clinically relevant, reproducible and simple to understand and to apply. Scoring will then be helpful to study series of patients and to evaluate the efficacy of new therapeutic strategies. However, a score does not replace the study of a liver biopsy and the generated numbers does not correspond to true measurements. Furthermore, its accuracy will always depend on adequate sampling. (Acta gastroenterol. belg., **2004**, 67, **290-293**).

Key words : grading, staging, semi-quantitative scoring, histopathology, chronic hepatitis, liver biopsy.

Introduction and background

Liver biopsy is a key element in the work-up of hepatic disease (1). In chronic hepatitis, it is the role of the pathologist not only to confirm the diagnosis and exclude any other eventual pathology, but also to define the grade and stage of this hepatitis. The grade corresponds to the degree of activity or severity of this hepatitis according to the level of inflammatory infiltrate and hepatic cellular lesions. The stage corresponds to the degree of hepatic parenchymal fibrosis. This morphological evaluation preconditions the therapeutic decision and also enables to control the treatment's efficacy.

The first classification of chronic hepatitis dates back to 1968, at a time when the aetiology of most chronic hepatitis was unknown (2). Based on histological aspect of the lesions, it differentiated persistent chronic hepatitis from chronic active or aggressive hepatitis, and later, from lobular hepatitis (3). Knodell, in 1981, was the first to propose a semi-quantitative estimate of the chronic hepatitic lesions, with the aim to evaluate series of biopsies and to follow the evolution under treatment on the basis of numbers rather than qualitative descriptions (4). This scoring system was based on the separate evaluation of four types of lesions : peri-portal necrosis and bridging necrosis (0 to 10), lobular necrosis (0 to 4), portal inflammation (0 to 4) and fibrosis (0 to 4). The sum of all the numbers obtained gave the final score, also called the histological activity index (HAI). This scoring system meant considerable progress and was very widely used, although it was subject to two major criticisms. It mixed the appreciation of the degree of activity to that of fibrosis, and it was not linear.

The explosion of knowledge in the realm of chronic viral and non-viral hepatitis in the past ten years led many groups to think about the ideal way to classify and stage chronic hepatitis. In 1994, the decision was taken to abandon the classification into chronic persistent hepatitis and chronic active hepatitis and to make a separate evaluation of grade and stage. Furthermore, the aetiology of hepatitis was also shown to be a better determinant of evolution than its classification (5). On the basis of these considerations, several newer scoring systems were formulated.

Newer scoring systems

Four different scores are now most often used by pathologists. The scoring systems of Scheuer (6), and of Ludwig (7,8) are simple. They are based on the evaluation of three types of lesions : portal and peri-portal activity (peri-portal necrosis and inflammatory infiltrate) graded 0 to 4, lobular activity (inflammatory infiltrate and necrosis) graded 0 to 4 and fibrosis graded 0 to 4 or 1 to 4 (Tables 1 and 2). In the METAVIR's scoring system (9-11), chronic hepatitis is classified according to the degree of activity (A : 0 to 3) and fibrosis (F : 0 to 4), evaluated separately. In terms of defining the degree of activity, the METAVIR group showed two lesions to be predominant : peri-portal necrosis and lobular necrosis. An algorithm enables the definition of the degree of activity by including these two types of lesions (Table 3). The different stages of fibrosis are illustrated in Figure 1. This scoring system, which was demonstrated to be reproducible, is widely used in France. In Belgium, it has been of application since the summer of 2002, when it was decided that treatment of chronic hepatitis C by pegylated interferon would only be reimbursed in case of a diagnosed fibrosis score F2 according to the METAVIR system. The last scoring system is the Ischak score (12) mainly used in English-speaking countries. It is particularly detailed and precise (Table 4) and represents a modification of the Knodell's scoring system.

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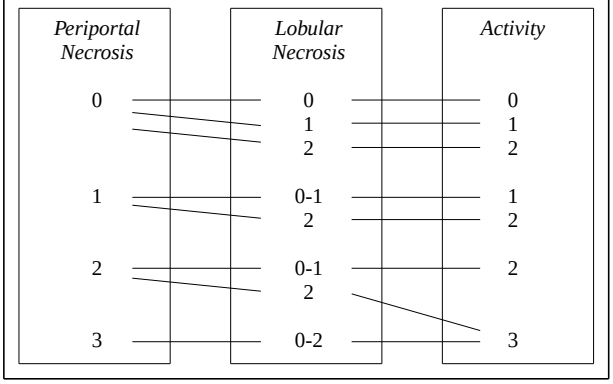
Table 1. — **The Scheuer system *(adapted from ref. 6)***

Portal/Periportal activity	
None or minimal	0
Portal inflammation only	1
Mild interface hepatitis	2
Moderate interface hepatitis	3
Severe interface hepatitis	4
Lobular activity	
None	0
Inflammatory cells but no hepatocellular death	1
Focal cell death	2
Severe focal cell death, with or without confluent necrosis	3
Damage including bridging necrosis	4
Fibrosis	
None	0
Enlarged, fibrotic portal tracts	1
Periportal or portal-portal septa but intact architecture	2
Fibrosis with architectural distortion but no obvious cirrhosis	3
Probable or definite cirrhosis	4

Table 2. — **The Ludwig system *(adapted from ref. 7 and 8)***

Portal	*Lobular*	*Grade*
None or minimal	None	0
Portal inflammation	Inflammation but no necrosis	1
Mild limiting plate necrosis	Focal necrosis	2
Moderate limiting plate necrosis	Severe focal cell damage	3
Severe limiting plate necrosis	Damage including bridging necrosis	4
Fibrosis		
None		0
Enlarged, fibrotic portal tracts		1
Periportal or portal-portal septa but intact architecture		2
Fibrosis with architectural distortion but no obvious cirrhosis		3
Probable or definite cirrhosis		4

Table 3. — **The METAVIR system : algorithm for evaluation of histological activity. 0 : none, 1 : mild, 2 : moderate, 3 : severe, except for lobular activity : 0 : none or mild, 1 : moderate and 2 : severe *(adapted from ref. 10)***



Interest and limitations of the scoring systems

Having the recourse to a histopathological code is very useful in patient follow-up, comparative studies and evaluation of new therapeutic strategies. Furthermore, the use of a simple and synthetic language favours better communication between pathologists and clinicians and constitutes an excellent research tool.

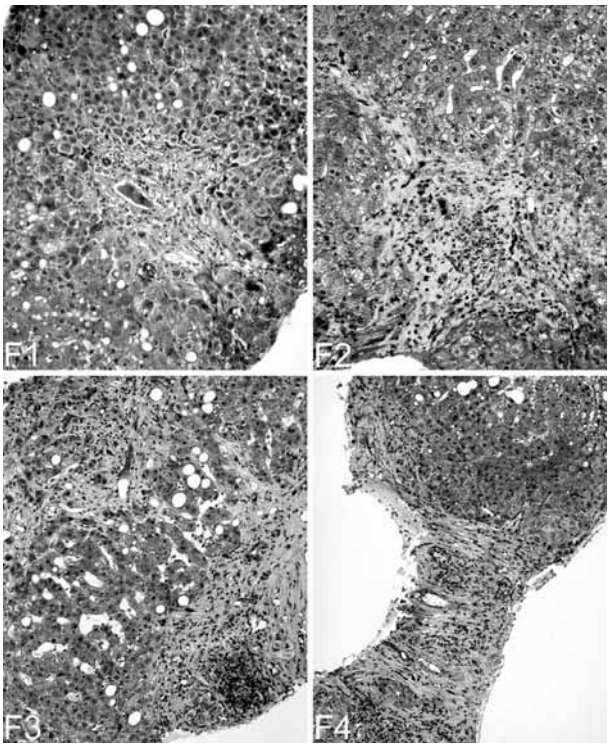


Fig. 1. — Fibrosis scoring according to the METAVIR system. (Masson's trichrome, X100) The stage F0, not illustrated, corresponds to the absence of fibrosis. F1 corresponds to periportal fibrosis, F2 to portal fibrosis with a few septa, F3 to septal fibrosis without cirrhosis and F4 to cirrhosis.

However, establishing a score alone cannot summarise the study of a liver biopsy (13-17). Indeed, the information a score brings is much more limited and reducing than a complete and carefully worded description. The conclusion of a liver biopsy will always have to include, beside the grade and stage of the chronic hepatitis both in a qualitative form and as a score, the elements in favour of the aetiology and the presence of possible associated lesions. The interpretation of a liver biopsy furthermore includes a subjective element and it would be troublesome to accommodate a quantification system that would be too precise such as for example based on the percentage of diseased territory (13). Finally, when evaluating data emanating from a semi-quantitative scoring system, it is important to understand the nature of the generated numbers. These numbers represent categories and not measurements, and this will have to be taken into account when performing statistical analyses (13-17). Moreover, each component of grading scores should be analysed individually.

The last problem to mention concerns sampling (18). Large samples are more comfortable for the pathologist but less safe for the patient. In view of the heterogeneous distribution of the lesions in diffuse liver disease such as chronic hepatitis, a semi-quantitative evaluation can only be achieved on a liver biopsy measuring 1 to 1.5 cm

Table 4. — **The Ischak system** ***(adapted from ref. 12)***

Periportal or periseptal interface hepatitis	
Absent	0
Mild	1
Mild to moderate	2
Moderate	3
Severe	4
Confluent necrosis	
Absent	0
Focal confluent necrosis	1
Zone 3 necrosis in some areas	2
Zone 3 necrosis in most areas	3
Zone 3 necrosis + occasional portal-central (PC) bridging	4
Zone 3 necrosis + multiple PC bridging	5
Panacinar or multiacinar necrosis	6
Focal apoptosis and inflammation	
Absent	0
One focus or less per 10x objective	1
Two to four foci per 10x objective	2
Five to ten foci per 10x objective	3
More than ten foci per 10x objective	4
Portal inflammation	
None	0
Mild, some or all portal tracts	1
Moderate, some or all portal tracts	2
Moderate/marked, all portal tracts	3
Marked, all portal tracts	4
Architectural changes	
No fibrosis	0
Fibrous expansion of some portal tracts	1
Fibrous expansion of most portal tracts	2
Idem with occasional portal-portal (PP) bridging	3
Idem with marked PP and/or PC bridging	4
Marked bridging (PP and/or PC) with occasional nodules	5
Cirrhosis, probable or definite	6

containing at least 6 to 8 portal tracts (1,19). Criteria are less strict with regard to transjugular biopsies, but their analysis is also more difficult and less reliable. Albeit, Regev et al. have shown differences of at least one stage and one grade between biopsies taken in the left lobe and those taken in the right lobe of the liver in one third of a series of patients suffering from chronic viral hepatitis C (20). The problem of sampling remains thus difficult. Two recent studies, specifically dedicated to the analysis of the adequate size of a liver biopsy for grading and staging chronic hepatitis, recommend larger specimen sizes (21,22). The first study showed underestimation of disease severity when evaluating small or slender biopsies and recommended taking specimens of at least 20 mm long, 1.4 mm wide with 11 complete portal tracts (21). The second study, only devoted to the reproducibility of staging in chronic hepatitis C, recommended a length of 25 mm (22). Morphometry of fibrous tissue, based on computer-assisted image analysis, may offer an alternative approach to staging, giving objective measurements (15,22). However, it is time-consuming and requires a special expensive equipment. Moreover, staging will not only evaluate the amount of fibrosis but also the presence of architectural modifications, not considered by morphometry.

Choosing a scoring system

In choosing a scoring system, there are some elements which are of particular importance (13,15-17,23).

In routine practice, scoring should only be performed when it presents a clinical interest. It should also ideally have a prognostic interest, and be adaptable to all chronic hepatitis. Theoretically, the choice of one system or another should be left to the preference of the clinicians and pathologists after having discussed together the purpose of scoring and the pathologist should be trained to use the scoring system.

One has to choose a scoring system that has proved its inter- and intra-observer reproducibility, which is the case for the four scoring systems detailed here. The notion of the reproducibility of a classification is particularly important in the evaluation of disease evolution or treatment efficacy. However, one should keep in mind that inter- and intra-observer variation will never be completely eliminated because grading and staging are essentially subjective.

The scoring system should be linear and sufficiently simple to understand and apply, in order to enable its use by all pathologists, whether they be specialists or not. In general, the simpler the system, the more reproducible. A more complex system, on the other hand, is often more precise and will detect small differences in liver damage or fibrosis. One could therefore opt for a simple system for routine analyses and for a more detailed system for research purposes. If necessary, an existing system may even be modified for an individual project. When performing a special study, two observers are recommended and they should have agreed on criteria beforehand.

Conclusions

Histopathology must provide information that is both reproducible and clinically relevant and all scoring systems have been stepping stones in that direction. The choice of one particular scoring system depends on the aim of the work. For routine diagnostic practice, a scoring system will only be effective if it is clinically useful and both easily understandable and applicable. Scoring accuracy is limited by the sampling and will never replace the detailed histological description.

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