

**ROLE OF AETIOLOGY IN THE PROGRESSION, REGRESSION, AND PARENCHYMAL
REMODELLING OF LIVER DISEASE
IMPLICATIONS FOR LIVER BIOPSY INTERPRETATION**

THE INTERNATIONAL LIVER PATHOLOGY STUDY GROUP

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Abstract

Clinicopathological concepts on acute and chronic liver disease have rapidly evolved over the last few years, with advances in general and specific treatment options, and improved patient outcomes. The old paradigm of “irreversibility” of cirrhosis had been challenged in major ways, and the validity of the usage of the term “cirrhosis” has come into question. This paper addresses aetiology-based clinicopathological concepts and features that may deserve attention because they may determine disease outcome and specifically patterns of regression and remodelling. A variety of therapeutic interventions may influence remaining disease features after elimination of damaging agents (virus, alcohol etc.), and determine the final clinical outcome including the risk of HCC. New concepts create new responsibilities and opportunities for the pathologist to contribute to the understanding of liver pathology and communicate this with clinical colleagues and researchers.

For some 200 years the prevailing concept in liver disease was that whatever the nature of persistent chronic injury to the liver, it would lead to irreversible damage, characterized by deposition of fibrous tissue and an attempt to regenerate. This condition was given the name “cirrhosis”.

Recently, we discussed the need to abandon this increasingly obsolete term (1).

Clinicopathological concepts have rapidly evolved since advances in general and specific treatment options, have led to improved clinical outcomes. Hence, the paradigm of “irreversibility” of cirrhosis has been challenged. The term “cirrhosis” is utterly confusing for the public at large including the fact that it can be applied to liver diseases which have not yet reached an advanced stage(2). The present paper examines the further implications of these newer perspectives on “cirrhosis” for pathologists, clinicians and researchers in the field of liver pathology.

The evolving role of the pathologist in chronic liver diseases.

As indicated, clinicopathological observations in patients with chronic liver disease have shown that treatment or removal of the causative injury often results in regression of fibrosis, parenchymal recovery and clinical improvement (3-6). The purely morphological definition of cirrhosis as bridging fibrosis and nodular parenchymal regeneration does not correspond necessarily to irreversible end stage liver disease. Alteration of the vasculature relationships, and in particular the formation of porto-central shunting vessels(7) , may no longer be the “bridge too far” that marks the point-of-no-return(8). The morphologic concept of the hepatic repair complex proposed by Wanless and colleagues(3), provides the basis for discerning differences between a progressive phase of hepatic damage, versus a regressive phase as illustrated in Table 1. The original description of the hepatic repair complex(3) included the following “regression parameters”: delicate perforated fibrous septa, isolated thick collagen fibres, delicate periportal fibrous spikes, portal tract remnants, hepatic vein remnants with prolapsed hepatocytes, hepatocytes within portal tracts or splitting septa, minute regenerative nodules, and aberrant parenchymal veins.

Therefore, the validity of the term “cirrhosis” as an indicator of end stage liver disease has come into question, and our recent proposal(1) to discontinue its usage altogether has already received some support in the hepatology community(9). Based on the principle that “advanced stage chronic liver disease” replaces “cirrhosis”, patients should be managed through the integration of clinical and pathological data indicating the likelihood of reversibility and recovery. The role of the liver pathologist therefore changes from the traditional grading and staging task, to providing a more nuanced assessment of whether the liver disease is in a progressive state, or is showing features of regression (Table 1). Furthermore, novel approaches to the histological quantification of collagen(10-12) offer morphological correlates to clinical measurements of portal hypertension, and provide new tools to revisit our understanding of the morphological signs of the “point of no return”(8, 13).

In our recent proposal(1) we have stressed the effect of the underlying aetiology in dictating the pattern and rate of scarring and regeneration. The pathologist must recognize the fundamental histologic features of a specific disease process, while simultaneously attempting to assess the dynamic balance between the deposition of extracellular matrix in the setting of disease progression (with potential collateral histologic features of portal tract and septal inflammation and parenchymal hepatocellular damage) or extracellular matrix reabsorption (as evidenced by minimal-to-absent portal tract or septal inflammation, and/or minimal-to-absent ongoing parenchymal damage). This dynamic balance depends not only on the interplay of innate and adaptive immune responses, and chemical mediators with stellate cells and portal myofibroblasts, but also on the pace of hepatic regeneration, and remodelling during recovery (14). Most importantly, the natural history of chronic liver disease is complex, and depends very much on the time course and nature of its aetiological stimulus and, more than before, on the outcome of specific therapeutic measures. This in turn dictates the topography of liver injury, the efficacy of the reparative response, and the risk of superimposed events, and complications such as the development of hepatocellular carcinoma. Co-existence of multiple aetiologies can add a further layer of complexity. There is a common basis to fibrosis progression, regression and remodelling, but, depending on the underlying cause, the dynamism of liver injury, parenchymal and vascular remodelling, parenchymal regeneration and recovery varies considerably, and so do its morphological correlates. All chronic liver disorders have a natural course in which disease activity may wax and wane, some diseases more accentuated than others, in terms of flare intensity, frequency, duration, and extent of parenchymal injury. Repair, regeneration, remodelling, all follow each episode and perhaps are more accentuated later in the course of the disease when architectural distortion becomes complicated by secondary vascular disturbances. This variable course may be substantially altered by more effective therapies now available. A liver pathologist attempting to gauge the severity of the disease and estimate features of progression or regression needs to be aware of the variable potential for topographical and chronological sampling error that each type of liver disease carries within.

The risk of error related to the specimen characteristics has mainly been addressed in the setting of grading and staging chronic viral hepatitis (15), in which increasing the length of liver biopsy decreases the risk of underestimating the hepatitis grade and stage. Biopsy length of at least 2-3 cm or the presence of 11 complete portal tracts, are considered adequate in this setting(16). Consequently, evaluation of any changes in the histological stage of fibrosis may be affected by sampling error: any progression or regression of fibrosis might indeed be biased by the inconsistent size of the paired liver biopsy samples (that is, small initial versus large follow-up biopsy; or vice versa (17)). How the sample size may affect the assessment of features related to regression/remodelling of advanced fibrosis stage (i.e. features referred to as “hepatic repair complex” by Wanless and colleagues (3)), has not been studied yet.

Regardless of the underlying cause, any advanced stage chronic liver disorder can be precipitated by a sudden event leading to acute liver dysfunction, multiorgan failure and death. The term acute on chronic liver failure (ACLF) has been proposed to describe this abrupt deterioration. Its histological correlates are still poorly defined(18).

With these considerations in mind, we examine in the following paragraphs some commonly observed liver disorders, as examples of how the pattern of progression and regression of liver injury can change between different aetiologies and influence variably the pathologists' perception of disease severity on liver biopsy specimens at different stages of the disease. Tables 1, 2 and 3 and figure 3 provide a summary of our discussion.

Patterns of disease evolution

Acute liver injury.

Acetaminophen overdose is a typical example of a single, sudden, diffuse, severe parenchymal insult. The toxic injury affects primarily hepatocytes, sparing large bile ducts and large vascular structures. The injury involves the parenchyma in a diffuse and homogenous fashion. At microscopic level, the injury usually affects the perivenular- to midlobular hepatocytes (acinus

zones 3 and 2), leaving a periportal rim of surviving hepatocytes. There are variable degrees of inflammation. The vascular anatomical relationships are preserved. The initial phase is characterised by reticulin stromal confluent collapse, colonisation of the injured tissue by leukocytes, and expansion of the residual hepatocellular plates sustained by a burst in hepatocyte proliferative activity. The resulting histological appearance in the first few weeks after injury is characterised by micronodules of regenerating parenchyma surrounded by bridging septa of condensed reticulin and variable degrees of gradually resolving inflammation. In the following months, the expansion of the hepatocellular plates is accompanied by thinning of the bridging septa and gradual restoration of the lobular integrity. Serial biopsy studies of survivors or native livers following auxiliary transplantation have shown how the hepatic architecture is restored (19, 20). There are restored hepatocellular plates cut across in places by slender incomplete reticulin septa reminiscent of some aspects of the hepatic repair complex described by Wanless and colleagues in chronic liver injury (3). Other factors contributing to repair in this context, including the role of progenitor cells and the degree of ductular reaction indicative of activation of this cell compartment have not been fully investigated (20-22). Similarly, in intermittently active chronic liver disease or acute-on-chronic liver injury, acute hepatitic episodes may be followed by more quiescent phases of recovery and remodelling. In patients treated by auxiliary transplantation, the residual native liver grows back to compensate for the initial loss, after which immunosuppression can be suspended with atrophy of the graft and return to normal liver function (20).

Chronic liver disease.

Alcoholic liver disease

Individual predisposition, drinking patterns and cofactors influence the rate of progression of alcoholic liver disease. Animal models have considerable drawbacks in reproducing the drinking patterns in humans (23) and thus do not consistently correlate to the histological findings in

human disease evolution. At macroscopic level the changes are distributed homogeneously throughout the organ, although instances of focal steatosis or lack of steatosis are described in the literature.

The predominant fibrotic changes begin, like the steatosis and steatohepatic changes, in the perivenular region (acinus zone 3), extending toward the portal tracts with increasing duration or severity of injury (24). There is sclerosis of central veins and perisinusoidal (also called “pericellular”) fibrosis, namely, collagen deposition in the space of Disse, along sinusoids and isolating individual or small clusters of hepatocytes. With progression, there is an ever more prominent “chicken wire fence” pattern of fibrosis, eventually linking central veins to portal tracts. Geographically alternating regeneration and atrophy of the trapped hepatocytes within these fibrous webs will eventually lead to compression of scar into central-portal fibrous septa and nodules of regenerating parenchyma without scar. However, with continued alcohol exposure, these unscarred areas then undergo the same process of injury and perisinusoidal scarring. The constant subdivision of new, regenerative nodules into smaller units is what leads to the classic “Laennec (micronodular) cirrhosis”(Figure 1a).

Large biliary or vascular structures are usually spared, with the exception of secondary involvement, for example by cardiac dysfunction, chronic pancreatitis or peribiliary gland ectasia (25). Of note, clinical signs of portal hypertension may be present before parenchymal nodular transformation takes place. A study based on paired biopsy obtained in heavy drinkers demonstrated the stage of fibrosis as independent predictor of further fibrosis progression and development of alcoholic hepatitis (AH), the most severe form of alcoholic liver disease (26). With the aim of constructing a histologic scoring system for prognosis of patients with alcoholic hepatitis (AH), a clinical syndrome of jaundice and liver failure that generally occurs after decades of heavy alcohol use (27), Altamirano and colleagues (28) identified that advanced fibrosis, presence of ductular and/or canalicular plus hepatocellular cholestasis, absence of neutrophil infiltration and megamitochondria were associated with short term survival (28).

With abstinence from alcohol use, the histological pattern of regression depends on which stage of histological injury is reached in the first place, bearing in mind that portal hypertension does not

correspond necessarily to effacement of the vascular anatomical relationships (Figure 2). It may even be related to hepatocyte necrosis and neutrophilic inflammation (29). A liver biopsy following a period of abstinence should be representative in identifying signs of improvement with regression of hepatocellular degenerative changes, reabsorption of fibrosis, and reduction in inflammatory infiltrates. Several authors (30, 31)(32) however, have described increasing proportion of lymphocytes in follow-up biopsies after abstinence.

At advanced stage, signs of remodelling can be observed. By comparing an initial liver biopsy with the appearance of the whole liver at autopsy at a median of 27 months afterwards, Fauerholdt and colleagues (33) showed conversion of a micronodular into a macronodular pattern in the majority of patients without significant difference in the conversion time, however, when comparing patients who stopped drinking, and those who continued (33), implying that remodelling can be a sign of, but not equal to, regression. Remodelling of a micronodular into a macronodular pattern has been replicated in rodents, following cessation of a 12 week CCl₄ treatment (34). The observations and components of reversal are dramatically reflected in the disease outcomes. Some truly deadly sick alcoholic patients with bleeding varices, ascites and profound jaundice (“endstage decompensated cirrhosis”) may survive in the end without transplantation. Comparison of autopsy livers of patients who died with active drinking to explanted livers from patients transplanted after 6 to 12 months of abstinence highlights this transformation from micro- to macronodules. In such regression there are many features of the hepatic repair complex, including thinning/compaction of fibrous septa with fragmentation; full regression of scar to restoration of normal function and resolution of portal hypertension has been reported(35).As depicted in Fig1A and 1B, delicate perforated septa, isolated thick collagen fibres, delicate periportal fibrous spikes and portal tract remnants suggest remodelling following abstinence.

Non-alcoholic fatty liver disease (NAFLD)

By and large, NAFLD in most adults shows the same histologic changes as seen in alcoholic injury. However, there are no approved drugs for the treatment of NAFLD. Lifestyle changes

based essentially on exercise and weight loss are the current therapeutic cornerstone and are less consistently successful compared to abstinence from alcohol. Nonetheless, studies on histological improvement after intervention exist and are based on comparison of NAFLD histological scores on pre and post-treatment paired liver biopsies. Dixon et al (36), for example, showed improvement of the histological features of NASH including regression of fibrosis in association with weight loss after gastric band placement. Histological improvement between paired biopsies was observed after weight loss following a hypocaloric diet and exercise (37). Pioglitazone (insulin sensitizers) improved all individual histological features (except for fibrosis) and achieved resolution of steatohepatitis – (currently considered the optimal surrogate endpoint in NAFLD trials (38, 39) more often than placebo.

Recently, the FLINT trial compared 25 mg of Obeticholic acid (OCA a synthetic bile acid with picomolar agonistic activity on farnesoid X nuclear receptor) vs. placebo over 72 weeks of therapy in non-cirrhotic NASH patients and reported improvement in all lesions of steatohepatitis including fibrosis, hepatocellular ballooning, steatosis, and lobular inflammation. A preplanned interim analysis showed improved histology in more patients on OCA (50 [45%] of 110) than on placebo (23 [21%] of 109). Importantly, there was a reduction in fibrosis score (one stage) in 35% of OCA-treated patients vs. 19% in the placebo arm (40). These are encouraging data that deserve confirmation in larger trials.

The natural history of -NAFLD and its histological counterparts, however, have not been fully elucidated. NAFLD may be a heterogeneous disorder. It should be noted that the most typical zonality of fibrosis observed in adults (perivenular/acinus zone 3) is different in paediatric populations in which the fibrosis is predominantly (but not always) portal (zone 1). Some adults show atypical patterns such as the non-zonal sinusoidal fibrosis described by Skoien and colleagues (41). These differences suggest that there may be multiple fibrogenic pathways involved. Recent studies (41, 42) have also suggested that periportal fibrosis in NAFLD is the result of a progenitor cell derived ductular reaction secondary to impaired hepatocyte regeneration. In their detailed study on the inflammatory cell infiltrate in NAFLD, Gadd and colleagues (43) have recently shown that early macrophage infiltration and subsequent portal

inflammation have a key role in NAFLD progression, possibly preceding the ductular reaction. Fibrosis progression is associated with arterialisation of centrilobular regions(44) and reticuloendothelial siderosis (45). NAFLD burns out towards its end stage (46, 47), and its histological end point overlaps with that of advanced cryptogenic chronic liver disease.

Haemochromatosis

Haemochromatosis is another example of parenchymal damage in which removal of the cause has been associated with regression of fibrosis or even reversal of advanced nodular stage (48-50). The liver parenchyma in advanced stage haemochromatosis is usually micronodular. The study by Falize and colleagues(50) was based on comparison of fibrosis Metavir scores between paired biopsies taken before and after venesection of C282Y homozygotes. Of 23 patients with F4 fibrosis in the first biopsy, the fibrosis score in the second biopsy was F0 in 1 patient, F1 in 4 patients, F2 in 3 patients and F3 in 2 patients. These findings do not exclude a conversion from a micronodular to a macronodular pattern. Similarly to NASH, iron loading of hepatocytes impairs their replicative capacity inducing a ductular reaction, which correlates with fibrosis progression and regresses after venesection (51). Different haemochromatotic genotypes may be associated with different histological phenotypes (52).

Wilson disease

Wilson disease can present clinically in many different ways and its natural history is largely unknown, with no clear correlation between its many different genotypes and its phenotype (53). It mimics histologically other liver disorders, overlapping, for example, with steatohepatitis at an early stage or simulating autoimmune hepatitis including positive autoimmune markers. In one series, most livers removed at transplantation for Wilson disease presenting with acute liver failure showed advanced stage liver disease, mostly in a micronodular pattern (54). Treatment with penicillamine and zinc to reduce copper accumulation result in a variable rate of histological improvement on serial liver biopsies (55), but perhaps data are too limited to draw any specific conclusions on the patterns of disease regression.

Autoimmune hepatitis

In autoimmune hepatitis the cause cannot be removed, but the immune response causing disease can be turned off by immunosuppression. In some instances the disease occurs without any symptom until the patient presents with decompensated advanced liver injury and ascites. The histology of a typical example of untreated disease reveals severe inflammation affecting the portal tracts, and associated with extensive interface and lobular hepatitis and usually some degree of the most severe hepatitis injury, i.e. confluent necrosis. Such necrosis may be perivenular only, may bridge between central veins and portal tracts, or so widespread as to cause mono- or multiacinar parenchymal collapse. Unlike in viral hepatitis, where the scarring appears to be independent of the geographic distribution of hepatitic foci, much of the fibrosis in autoimmune hepatitis seems to follow directly on the replacement of areas of confluent necrosis by scar.

The natural course is thought to fluctuate, with periods of quiescence alternating with flares of activity, sometimes of sufficient intensity to manifest clinically or even cause acute liver failure. Biopsy samples taken during a quiescent phase or after initiation of treatment show often much milder inflammation, frequently associated with slender, post-necrotic type fibrous septa. Review of paired liver biopsies showed an improved in fibrosis score according to the Ishak system in 53% of patients treated with corticosteroids (56). Dufour (4), as well as Serpaggi and colleagues (57) even suggested reversal of cirrhosis in a some cases. Examination of whole livers removed at transplantation tends to reveal a heterogenous pattern, with broad areas of parenchymal collapse and scarring alternating with expanses of preserved, more or less nodular parenchyma. This pattern probably reflects the alternating effect of injury, repair and regeneration, with remodelling occurring at variable rate in different parts of the organ and at different times. Sampling error thus appears inevitable when using liver biopsy to assess regression at an advanced stage and may limit its usage in directing immunosuppression withdrawal.

Chronic hepatitis C

Chronic hepatitis C is a slowly progressive persistent disease. Its progression rates towards advanced stage disease are variable and considered to be not linear (58). Confounders of outcomes include alcohol and NASH. A morphometric image analysis has suggested that the pace of fibrosis increases at advanced stages (59). The clinical course in untreated patients may be marked by usually asymptomatic flares of activity (60) and may be related to the virus genotype (61).

The virus can now be effectively eradicated, and sustained virological response (SVR) is achieved in the majority of patients (62). With the introduction of the new direct acting antiviral regimens, treatment should be focused on preventing the onset, and arresting or reducing the risk of advanced disease. The prevalence of upper gastrointestinal varices in patients with chronic hepatitis C is estimated as 16% in patients with Ishak stage 3 to 4 and 39% in patients with more advanced stage (58), and in whom SVR correlates with reduction in portal pressure measurement. Emphasis on the outcome measurement on patients with advanced stage liver disease has therefore implications on how pathologists stage advanced liver injury and identify signs of histological improvement. Comparison of semiquantitative fibrosis score on paired biopsies before and after treatment has been the conventional and traditional method of assessing tissue response to antiviral treatment. Its limitations are well known (18). D'Ambrosio and colleagues (63), have shown more recently that biopsies from patients with advanced stage chronic hepatitis C and SVR to antiviral treatment have reduced interface and lobular hepatitis, show features of stage regression, with reduction in collagen and thinning of fibrous septa, and show additional signs of improvement including reconstitution of the metabolic lobular zonation, and reduction of the progenitor cell response. Livers of patients with advanced stage chronic hepatitis C are characterised by broadly expanded fibrous septa and small regenerative nodules (64) of similar size and appearance, with preservation of the macroscopic lobar anatomical relationships (Figure 3). Pattullo and colleagues (65) have shown that SVR correlates with fibrosis regression when using a method combining semiquantitative fibrosis scoring and the qualitative features of parenchymal remodelling constituting the hepatic repair complex.

Chronic hepatitis B

In contrast to chronic hepatitis C, advanced stage chronic hepatitis B is characterised by larger regenerative nodules (7, 66) of variable size (Figure 1b). The reason is unknown. Flares of activity can occur spontaneously or during or after antiviral therapy (67), in relation or not to seroconversion (68) causing episodes of symptomatic severe parenchymal injury which could explain the macronodular pattern of advanced stage disease (69). Extensive hepatocyte clonal expansion could be a contributing factor. This has been observed in the early stage of chronic hepatitis B probably as the result of the selective targeting by the viral immunity of some hepatocyte populations and consequent survival and expansion of others (70, 71). Regardless of the precise mechanism involved, a macronodular pattern may affect the efficacy of a needle sample to be representative (8), and needs to be considered when evaluating post-treatment response (72, 73). However, a large number of cases of regression of HBV cirrhosis are now on record (72, 73) (74, 75). These studies report the grade and stage of chronic hepatitis B before and after prolonged antiviral therapy, but lack a detailed account of the histologic changes. However, the original description of the hepatic repair complex included 8 cases of chronic hepatitis B among other cases of chronic liver diseases(3), and it is our experience that the features of this complex are commonplace in liver biopsy and resection specimens of patients on long-term anti-HBV treatment (75).

Primary Sclerosing cholangitis (PSC)

Progression of fibrosis in biliary disorders differs from that of the diseases presented above. At an advanced stage, the fibrosis remains portal based, and the porto-central anatomical relationships may still be maintained, to the point that advanced stage chronic biliary disease has not been considered "true cirrhosis"(8). In addition, the dynamics of the process in PSC are particularly complex. There is considerable topographical variation, as large or small ducts, or a combination of the two, are variably affected, and a notable disparity in which different segments or lobes can be involved. Small duct cholangitis can result directly into peripheral portal-based and eventually

bridging fibrosis. Large bile duct cholangitis may affect the biliary drainage of large parenchymal areas, as well as cause “bystander” damage of portal veins leading to local perfusional defects. Hepatic vein phlebitis is often observed, indicating a possible component of outflow blockage. Episodes of ascending cholangitis, development of dominant biliary strictures and concomitant inflammatory bowel disease can also contribute to fluctuations in disease activity. Livers removed at transplantation often show large areas of atrophy and hypertrophy with intervening fibrous scarring, regenerative hyperplasia and active inflammation, resulting in a marked alteration of the lobar anatomy to almost full effacement in some cases, with extreme forms of segmental or even lobar atrophy and compensatory hypertrophy (Figure 1c and 1d and figure 3). Liver biopsy samples in advanced stage primary sclerosing cholangitis are likely to suffer severely from topographical and chronological sampling error if used to gauge the severity of the disease. There may be role in identifying histological signs of progression at an earlier stage. Granules of copper associated protein in periportal hepatocytes may be a possible marker of progression in otherwise minimal fibrotic liver with no biliary damages characteristic to PSC in needle liver biopsies (76).

Primary biliary cholangitis (PBC)

PBC is characterised by injury to small interlobular-septal branches in a more relatively diffuse fashion, without involvement of large bile ducts or veins. The disease activity is generally low, and progression slow and often steady, portal based, with preservation of the porto-central relationship often to a very late stage. In this particular context the dynamics are probably simpler than in PSC and revolve around a more simple fibrogenic/fibrolytic steady-state. Explant livers are often large, with relatively homogenous small parenchymal nodularity and preserved lobar anatomy. At microscopic level, the destruction of smaller bile ducts followed by cholestasis and fibrosis are known to occur slowly and steadily, although rather heterogeneously, so the combined assessment of these histologic features may be reliable to evaluate early to advanced stages of PBC and to identify features of regression

Vascular obliterative disorders

Vascular obliterative disorders are more similar to biliary disorders than to diseases affecting diffusely the hepatic parenchyma. The hypercoagulable state is a dynamic episodic process in which thrombotic bouts result in thrombotic obliterative lesions of different age scattered throughout the parenchyma, leading to secondary vascular obliterative phenomena, and eventually resulting in areas of atrophy, hypertrophy, nodular regenerative hyperplasia, portal-based or centrilobular scarring and what is eventually a complete disarray of the orderly lobular or acinar architecture. The chronological and topographical sampling error together with the fact that the cause cannot be removed essentially makes this type of pathology an unlikely candidate for monitoring progression or regression based on liver biopsy. The morphological overlap with aspects of the hepatic repair complex derives from the common denominator of vascular involvement.

Progression, regression, remodelling and hepatocellular carcinoma.

Regardless of the underlying aetiology, and the stage at which regression takes place, response to therapy does not eliminate the risk of developing hepatocellular carcinoma (HCC). While advanced stage liver disease has often been thought of as a precursor lesion to HCC, it is now clear that neoplastic transformation is a process that, like fibrosis, takes years to decades and runs its course in parallel with such fibrotic progression. Thus, regression of fibrosis does not undo the genetic and/or epigenetic changes that are part of the multistep process of human hepatocarcinogenesis (77). This has clearly implications in terms of long-term surveillance and clinical management strategies. It also challenges pathologists to investigate for features predictive of this risk. Cell growth through integrin signalling related to fibrillar collagen deposition, migration and antiapoptotic mechanisms of preneoplastic hepatocytes, have been proposed as some of the mechanisms associated with HCC development in post-SVR chronic hepatitis C (78).

Conclusion

New concepts on the reversibility of the pathological changes in advanced chronic liver diseases are having a major impact on patient management and in turn on the role of the liver pathologist, which evolves from the traditional grading and staging task, to a more sophisticated investigation of tissue biology dynamics, gauging of disease severity, progression or regression, hepatic regeneration and functional recovery. The chronological and topographical variability of the disease process depends very much on the underlying aetiology, and needs to be taken into account particularly when interpreting liver biopsy rather than resection specimens. Tables 2 and 3 and figure 3 provide a summary of how these concepts apply to common liver disorders at early and late stage. This in turn dictates how and when information derived from histological observations can be integrated into the clinical context, particularly in view of the continuously evolving and more individualised clinical practice and treatment scenarios.

Figure Legends:

Figure 1. Livers removed at transplantation for advanced stage chronic liver disease. A: Alcoholic liver disease. B. Chronic hepatitis B. C,D. Primary sclerosing cholangitis. In A and B the parenchymal surface is diffusely nodular, micronodular in A and more macronodular in B. The lobar anatomy is still intact. In A the small nodule size is similar throughout the organ. In B the nodule size varies and a liver biopsy sample may not be fully representative depending on the size of the nodule hit by the needle. The lobar anatomy is intact in both A and B. In contrast (C) the liver removed from the patient with primary sclerosing cholangitis shows a marked distortion of the lobar anatomy due to segmental or even lobar atrophy and compensatory hypertrophy and remodelling. It is almost impossible to recognise the normal anatomical landmark in this specimen. This is probably due to the episodic nature of the disease course, and the topographical variation of the biliary injury and secondary vascular compromise affecting different parts of the liver at different times. Picture D shows the cut section of the same liver demonstrating the marked variation in parenchymal nodular transformation in different segments (Picture C and D courtesy of Dr Corina Cotoi, King's College Hospital).

Figure 2. 62 year old with history of alcoholism. Drank heavily for 12 years, reduced markedly his alcohol intake in the following 16 years and stopped completely 12 months prior to transplantation. Hepatocellular carcinoma (HCC) was discovered during surveillance 3 years prior to liver transplantation and treated by loco-regional therapy. A second lesion was identified a few months before transplantation. The patient was clinically well at the time of transplantation with no signs of acute decompensation, hepatic encephalopathy, jaundice, variceal bleed or synthetic failure. HCC was the indication for liver transplantation.

The changes in his explant liver were quite variable. One sample (A-B, same field, H&E in A and reticulin staining in B) shows mild fibrosis in the form of slender fibrous septa. Another sample show broader septa and frank parenchymal nodularity.

Figure 3. The four quadrants in each diagram describe how the process of injury, regression and remodelling affects different regions of the liver over time. There is no specific reference to a particular segment or lobe, and the diagram is purely for the illustrative purpose of demonstrating geographical variation.

Left hand side diagram. Progression to advanced stage in some disorders occurs relatively gradually and homogeneously throughout the organ, in an 'ebb and flow' pattern without marked regional variation. More significant variations in progression, regression and remodelling probably occurs later in the course of the disease when secondary vascular phenomena set in. Chronic viral hepatitis is an example.

Right hand side diagram. In contrast to the previous example, progression to advanced stage liver disease, may occur, in some instances, in a heterogenous fashion with bouts of activity of variable intensity affecting different regions of the liver at different times. Progression, regression and remodelling in these regions is not synchronised and the end result is of a liver with marked distortion of the segmental and lobar anatomy. Primary sclerosing cholangitis is an example.

Liver biopsy interpretation in this context suffers from high chronological and topographical sampling error.

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