CASE REPORT

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Fibrosis Regression of Advanced Chronic Liver Disease Outlined by a Novel Histological Classification

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ABSTRACT

In the past, advanced chronic liver disease was considered irreversible, but with better understanding and improved treatments, it is now recognized that fibrosis is a dynamic process that can regress even when it has reached the stage of cirrhosis. We present the case of a 60-year-old male patient with advanced chronic liver disease due to chronic hepatitis B, whose follow-up liver biopsy revealed significant fibrosis regression after successful antiviral therapy. We confirmed the predominantly regressive pattern using the P-I-R classification, a new histological classification that defines the tissue features as predominantly "Progressive, Intermediate or Regressive" by comparing stroma to parenchymal ratios. Furthermore, we also point out the prognostic value of P-I-R classification, as the patient has remained free of decompensation over time. In this clinical case, we highlight important aspects of the pathophysiology and histopathology of cirrhosis regression, emphasizing its critical prognostic significance. Finally, familiarizing clinicians and pathologists with the application of the P-I-R classification may improve prognostication based on histology in patients with advanced liver disease.

Key words: cirrhosis regression – hepatitis B – P-I-R classification.

Abbreviations: aHSC: activated hepatic stellate cell; Ag: antigen; ACLD: advanced chronic liver disease; ECM: extracellular matrix; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HRC: hepatic repair complex; HSC: hepatic stellate cell; MMP: matrix metalloproteinase; P-I-R: Progressive, Intermediate or Regressive; VCTE: vibration controlled transient elastography.

INTRODUCTION

The term "advanced chronic liver disease – ACLD" refers to the clinical entity of patients with the late stage of chronic liver disease [1] and replaces the use of the term "cirrhosis", which is a histology-driven concept and corresponds to end stage of the disease [2]. Advanced chronic liver disease has been viewed as a progressive disease, yet in the last decade, a better pathophysiological understanding of liver fibrosis and improved treatment options have led to a change in this paradigm. Advanced chronic liver disease is now viewed as a dynamic process with the possibility of regression after elimination of the underlying disease causing liver injury [3]. For instance, the successful treatment of viral hepatitis or changes in lifestyle with notable weight reduction have been associated with regression of cirrhosis [4, 5].

Liver biopsy plays a key role in the diagnosis and assessment of liver fibrosis severity. To quantify the extent of fibrosis regression, paired biopsies have been essential. However, the definition of cirrhosis regression and how to establish the diagnosis are still a work in progress. Moreover, within the field of histological classifications of ACLD, regression is not routinely described. Nevertheless, Wanless et al. [6] described eight parameters deemed indicative of cirrhosis regression, collectively referred to as the "hepatic repair complex (HRC)". Recently, the HRC has been included in a novel classification called the P-I-R classification of the Beijing classification aimed at diagnosing cirrhosis regression [7]. The P-I-R classification defines the histological tendencies of predominantly "Progressive, Intermediate or Regressive" fibrosis [7]. Recently, it has been demonstrated that the P-I-R classification obtained from a single on-treatment biopsy (at least >1 year of antiviral therapy in patients with chronic hepatitis B) allows the gathering information about the dynamic trends of fibrosis

without the need for serial biopsies, and that it also correlates with prognosis in patients with cirrhosis [8].

Since the P-I-R has not yet entered clinical practice in Europe, we analyzed the findings and P-I-R of a patient with chronic hepatitis B-related advanced chronic liver disease who presented clinical and histological regression after successful therapy.

CASE PRESENTATION

A 60-year old male with a medical history of dyslipidemia and cholecystectomy presented to our center with elevated transaminase levels persisting for the past two years. The initial laboratory data revealed a mixed pattern elevation of transaminases (aspartate aminotransferase 208 U/l, alanine aminotransferase 265 U/l) and cholestasis parameter (alkaline phosphatase 91 U/l and gamma-glutamyl transpeptidase at 105 U/L). He had no history of alcohol intake, medications, needle stick injury, drug use or travels to foreign countries. At the first consultation, he reported only general fatigue and the physical examination was normal with no signs of obesity or other relevant findings.

Laboratory tests were positive for chronic hepatitis B virus (HBV) infection with HBs antigen (Ag) and HBeAg positivity and HBV DNA 4,217,950,000 IU/ml. Other viral infections and other common causes of liver disease were excluded by further laboratory examinations.

On ultrasound the liver showed nodular liver contour and enlarged caudate lobe without signs of portal hypertension and without focal liver lesions (Fig. 1). An esophagogastroscopy was performed, which revealed no evidence of varices. Liver stiffness [using vibration controlled transient elastography (VCTE), Fibroscan®, Echosens, France] was elevated (24 kPa). Therefore, to determine the extent of parenchymal inflammation and refine fibrosis staging, a liver biopsy was proposed and conducted. The biopsy (Fig. 2) showed typical signs of active chronic hepatitis B virus infection alongside with advanced portal fibrosis (bridging fibrosis), corresponding to a METAVIR of F3 [9]. On immunohistochemistry, the HBsAg was found in 80% of the hepatocytes. The patient was started on antiviral treatment with Tenofovir disoproxil 245 mg per day. Follow-up every 6 months included ultrasound examination as a part of hepatocellular carcinoma (HCC) screening, liver stiffness measurement using VCTE, and blood tests monitoring transaminases, liver function and HBV DNA by PCR.

Over the course of the following years, the patient responded well to the antiviral therapy without developing any resistance to the antiviral therapy. The HBV DNA reflected the successful treatment by decreasing the viral load and stabilizing it to values <20 IU/ml. In addition, it was observed early on that the patient underwent a HBeAg seroconversion alongside with the reduction of an initial HBsAg titer of 125,000 IU/ml to 2343 IU/ml. Similarly, liver stiffness decreased from initial 24 kPa to 3.6 kPa after 4 years and maintained stable. His clinical course was uneventful (no focal liver lesions, no reactivations of hepatitis B, no signs of portal hypertension or liver decompensation episodes).

After four years of continuous antiviral treatment and aforementioned clinical improvement a second liver biopsy was performed.The Hematoxylin and Eosin (H&E) staining showed a minimal non-bridging portal fibrosis and a reduction of the METAVIR to F1, demonstrating that the patient had important

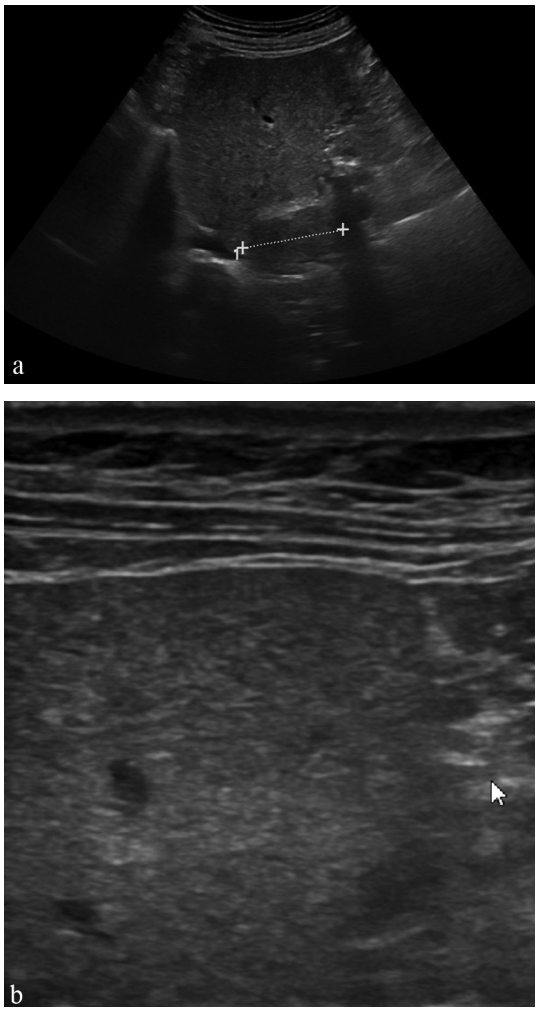

Fig. 1. Ultrasound findings suggestive of advanced liver fibrosis in the patient showed a) changes in volume distribution including an enlarged caudate lobe and b) nodular liver contour with inhomogeneous liver parenchyma with the linear probe.

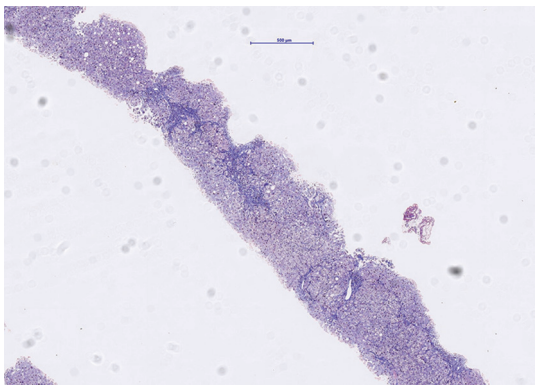

Fig. 2. Pre-therapy biopsy Chromotrope Aniline Blue (CAB) staining, showing an advanced stage of liver fibrosis with bridging fibrosis, with areas displaying the close proximity between the central vein and the portal fields. Staged METAVIR A2, F3. It shows >50% of fibrous septae are wide/broad and sparsely aggregated collagen fibers, P-I-R classification: progressive.

regression of his liver fibrosis. The P-I-R classification applied to the second biopsy after four years of therapy showed a P-I-R predominantly regressive pattern (Fig. 3).

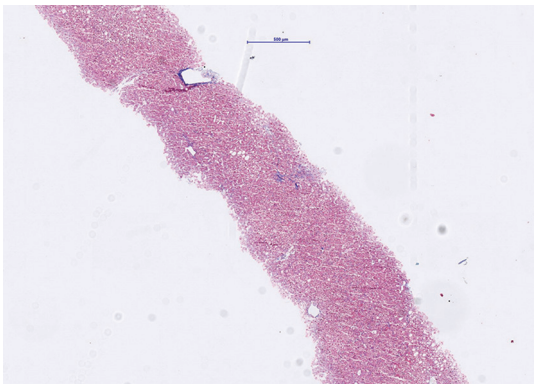

Fig. 3. Follow-up biopsy on ongoing antiviral treatment (4 years) Chromotrope Aniline Blue (CAB) staining, showing a minimal portal fibrosis with no septal fibrosis. Staged METAVIR A0, F1. It shows >50% show features of term "hepatic repair complexes" with repopulation of hepatocytes and delicate perforated fibrous septa, P-I-R classification: Regressive.

During the follow-up, the patient has shown an excellent outcome. He has undergone regular controls and has not experienced any liver-related events. The medication is well tolerated by the patient and the virus load remains negative under 10 IU/ml.

DISCUSSION

This case report demonstrates that ACLD is a reversible condition, resulting in regression of fibrosis even to a minimal stage. An intriguing aspect of fibrosis regression is that despite the efficacy of an etiologic therapy on the cause of liver disease, some patients do not experience fibrosis regression. This suggests that other factors influence fibrosis regression and its clinical consequences. Recently, we have confirmed that diabetes mellitus, obesity and high liver stiffness before treatment are associated with a lower likelihood of fibrosis regression [10]. Other factors that have been proposed include the cross-linking of collagen and elastin, which produce acellular areas that may increase the resistance to degradation of collagen [11]. Furthermore, patients exhibiting thick fibrous septa and vascular changes on histology are hypothesized to hinder fibrosis regression [11-13]. Consequently, the degree of fibrosis improvement appears to be highly dependent on the pre-treatment stage of fibrosis [14]. However, "the point of no return" at which regression will not occur is still undefined [15].

The regression of liver fibrosis presupposes the cessation of this process with the interruption of active scar formation along with decrease in activated hepatic stellate cells (aHSCs) and remodeling/removal of extracellular matrix (ECM) [16, 17]. Additional activation of collagenolytic mechanisms is also observed in liver regression. Collagen degradation requires the activation of matrix metalloproteinases (MMPs), which are important matrix-degrading enzymes. Along with other signaling pathways, MMPs also induce aHSC apoptosis [16, 17].

Kisseleva et al. [16] conducted a study on an animal model of fibrosis regression and demonstrated that the decrease of aHSCs is essential for the resolution of liver scarring and that the reduction in ECM is associated with the regression of fibrosis. Furthermore, they propose different "cellular fates" that aHSCs might undergo during the liver fibrosis regression: cell apoptosis, inactivation, or cellular senescence. About half of the aHSC in regressive fibrosis liver parenchyma follow a complex interaction of pro-apoptotic and pro-survival signaling pathway and end in programmed cell death, apoptosis. Given the dynamic differential potential of aHSC, some revert to an inactive state, thus bypassing apoptosis. The inactivated HSC are not identical to physiologically quiescent HSC and can potentially differentiate back to aHSC/myofibroblasts more rapidly. However, the biology of HSCs during fibrosis regression is not fully understood, and in particular, there is an ongoing controversy regarding the role of senescence in this setting. The exact contribution of senescent HSCs to fibrosis and cancer is debated [17-19].

Regarding the histopathological features of regression, Wanless et al. [6] in 2000 first defined histological parameters describing regression of cirrhosis. They introduced the term "hepatic repair complex" (HRC), observed independent from etiology in livers showing fibrosis regression. Among the eight features composing the HRC, four refer to stroma to parenchymal characteristics, such as hepatocytes within splitting septa, isolated thick collagen fibers, delicate perforated fibrous septa and delicate periportal fibrous spikes. The further three HRC describe vascular modifications such as hepatic vein remnants with prolapsed hepatocytes, aberrant parenchymal veins, and portal tract remnants. Finally, the appearance of tiny regenerative nodules, so called "buds", defines the last distinctive histological hallmark. These "buds" are hepatocytes, proliferating ductules and CD34-positive endothelial cells. These CD34-positive cells remain visible as solitary vascular channels and indicate previous regions of extinction. The publication also defines regression as a dual process including the elimination of fibrosis and the repopulation of hepatocytes in damaged areas.

Sun et al. [7, 8] recently proposed an updated classification to be used in patients with HBV, including specific histopathological characteristics. The "Beijing classification" employs the terms Progressive, Intermediate, and Regressive (P-I-R classification), to describe the dynamic changes of liver fibrosis. This new classification defines predominantly fibrotic regressive changes when the majority (more than 50%) of fibrous septae show features of HRC, with thin and densely compacted stroma. Predominantly progressive fibrosis is described when more than 50% of fibrous septae are wide/broad, sparsely aggregated collagen fibers, along with inflammatory cells. The indeterminate stage comprises results with simultaneous appearance of progressive and regressive characteristics, therefore no final majority on the fibroseptal characteristics is established.

One study [8] has assessed the clinical applicability and prognostic value of the P-I-R classification and analyzed the possibility of assessing it on a single on-treatment liver biopsy. The results suggest an association of fibrosis regression with a decreased risk for liver related events, specifically

hepatic decompensation [8]. Therefore, this new histological classification holds prognostic potential in hepatitis B patients.

It is important to mention that the current recommendations [8] suggest continuing screening for HCC in all patients with chronic hepatitis B and advanced chronic liver disease, including those classified as regressive on treatment. Due to various oncogenic and epigenetic alterations resulting from viral DNA integration, follow-up screening for HCCs remains crucial. Moreover, the P-I-R classification is limited by the heterogeneity in the distribution and severity of fibrosis within the liver, making it susceptible to sampling bias during liver biopsies. Additionally, a significant limitation of the P-I-R classification is its specificity to etiology, as it was primarily developed and validated in patients with HBV-related liver fibrosis. Recent research sparking hope to its applicability on patients suffering from hepatitis C [20]. However, further investigations are needed to determine the applicability of the P-I-R classification for patients with liver cirrhosis caused by other etiologies.

CONCLUSION

The presented case of cirrhosis regression highlights some novel aspects related to the diagnosis on histology of this important endpoint. The successful application of the P-I-R score using the "Progressive, Intermediate or Regressive" pattern, in this case report emphasizes the value of adopting this novel histological classification in similar cases to guide the histological diagnosis, management and follow-up. Notably, the association between fibrosis regression and a reduced risk of liver-related events, particularly hepatic decompensation, highlights its clinical relevance. Then, advances in histopathological diagnosis will improve the prognostic stratification of patients with advanced chronic liver disease receiving etiologic therapy.

Conflicts of interest: None to declare.

Authors' contributions: Y.P.M. and A.B conceived and designed the study. M.D. collected the data and drafted the manuscript. M.M. collected the histological images and revised the manuscript. J.B. critically revised the manuscript. All authors read and approved the final version to be published.

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