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The utility of repeat liver biopsy in autoimmune hepatitis: a series of 20 consecutive cases

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Summary

Liver biopsy is recommended to establish the diagnosis and to assess remission in autoimmune hepatitis (AIH) patients. The aim of our study was to assess the utility of repeat biopsy in AIH. Forty liver biopsies from 20 consecutive AIH patients who underwent repeat biopsy were evaluated. We assessed the biopsies for histological findings other than AIH and how often the repeat biopsy led to a change in clinical management. Furthermore, we correlated the changes in the laboratory findings with the histological features. AIH patients in the study were mostly female (80%; average age 58.7 years). The most common indications for repeat biopsy included elevated transaminases (40%) and evaluation prior to treatment alteration (40%). Seventy percent of the patients showed improved aminotransferase levels, which demonstrated no significant correlation with the inflammatory ($p = 1.000$) or fibrosis progression ($p = 0.116$). Forty percent of the patients showed pathology other than AIH in the repeat biopsies (3 steatohepatitis; 5 cholangiopathy features). Changes in the management were seen in all patients. Repeat biopsy is important in AIH patients as aminotransferase levels are not always a reliable marker for inflammatory and fibrosis progression. Moreover, liver biopsy is an effective method for diagnosing comorbid liver conditions.

Key words: Autoimmune hepatitis; liver fibrosis; biopsy; primary biliary cirrhosis; steatohepatitis.

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INTRODUCTION

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease of unknown cause which, when untreated, leads to advanced fibrosis and liver failure. The 2010 guidelines from the American Association for the Study of Liver Diseases (AASLD) recommends liver biopsy examination at the time of presentation to establish the diagnosis and to guide the treatment decision. Furthermore, the goal of initial management includes improvement of histological evidence and laboratory indices of these patients.[1]

Liver biopsy, the gold standard for evaluation of chronic hepatitis and fibrosis, has several limitations. The small biopsy only represents a small area of the entire liver and focal histological abnormalities may be missed. In a study looking at the diagnostic yield of percutaneous needle biopsy, Maharaj *et al.* reported that sampling variability was seen in approximately one half of cases with cirrhosis, hepatocellular carcinoma, and metastatic carcinoma.[2] Inter-observer and intra-observer variability is also common in histological evaluation. Finally, liver biopsy is an invasive procedure which involves minor and major complications with reported mortality risk of 0.01%.[3]

Non-invasive markers of liver fibrosis have been developed rapidly in recent years. Non-invasive methods for assessing liver fibrosis include combinations of routine laboratory tests, fibrosis biomarkers, and advanced imaging techniques such as transient elastography and acoustic radioscan force impulse. The lack of a gold standard to validate the tests remains the main problem in the development of these methods.[3] The majority of these scoring systems were developed to assess fibrosis in patients with chronic hepatitis C. The reliability of these non-invasive markers in AIH patients has not been reported.[4,5]

Several publications have challenged the significance of performing liver biopsy in AIH patients. A retrospective study evaluating 257 AIH patients reported that the vast majority of patients with typical laboratory features of AIH were likely to have compatible histological findings in the biopsy and a few cases with atypical histological findings did not have a significant impact on patient management.[6] Another study of 82 AIH patients showed that normalisation of serum parameters [alanine aminotransferase (ALT) and IgG] was associated with patients who were at low risk of fibrosis progression despite the fact that laboratory indices were not reliable to predict complete histological remission.[7]

The aim of this study was to assess the importance of repeat liver biopsy in a series of AIH patients by looking at the prevalence of histological abnormalities seen on the serial biopsies and how these biopsies altered the management of these patients.

METHODS

Patient selection and clinical information

Twenty consecutive patients with AIH who underwent repeat liver biopsies at our institution in a 5-year period (2009–2014) were selected for our study. Diagnosis of AIH for these patients was made by the clinicians based on the clinical, laboratory, and histological findings. Two biopsies from each patient were retrieved for evaluation. Demographic information and aminotransferase levels were recorded. Other laboratory indices (gamma-globulin or IgG levels) were excluded from analysis because the information was not

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available in some of the patients (several patients were referred from outside institutions). Indications for repeat biopsies and changes in the management were reviewed by a hepatologist (AT). The indications for these biopsies were categorised into three groups: increased liver function tests, treatment-related indications (histological evaluation prior to stopping or lowering the immunosuppressant drugs), and others (restaging fibrosis or diagnostic clarification). This study was approved by Committee for the Protection of Human Subjects at Dartmouth College.

Liver biopsy

Liver biopsies were reviewed by two pathologists (JP and AAS) simultaneously. Biopsy cores included in the study were at least 1 cm in length and consisted of more than six portal tracts to satisfy adequate evaluation. Each case consisted of two levels of haematoxylin & eosin (H&E) and Masson's trichrome-stained slide, and was assessed for histological diagnosis, degree of inflammation and fibrosis. Inflammation and fibrosis were evaluated using the semi-quantitative Scheuer system.[8] The grading system includes the assessment of portal/periportal and lobular inflammatory activities: 0, none/minimal inflammation; 1, inflammation without necrosis; 2, focal/mild interface necrosis; 3, moderate interface necrosis; 4, severe interface necrosis including bridging necrosis. Meanwhile, the fibrosis staging was based on the areas with the highest degree of fibrosis: 0, no fibrosis; 1, enlarged, fibrotic portal tracts; 2, periportal septa with intact architecture; 3, bridging fibrosis; 4, cirrhosis.

Baseline liver biopsies were further classified into three categories based on the histological criteria established by the International Autoimmune Hepatitis Group (IAIHG): patients with typical histology, histology compatible with AIH, and atypical histology.[9] The typical histological features of AIH include interface hepatitis with lymphoplasmacytic infiltrates in the portal tracts extending into the lobules, emperipolesis (active penetration by one cell into and through a larger cell), and hepatic rosette formation. The presence of all three histological features was a requirement for the group of patients with typical histology. Compatible features were chronic hepatitis without the presence of all typical features, and the histology was considered atypical when it showed findings of another diagnosis such as primary biliary cirrhosis or steatohepatitis.

AIH-primary biliary cirrhosis (PBC) overlap syndrome

Patients with AIH-PBC overlap syndrome were diagnosed using Paris criteria, which require the presence of two of the three criteria for each diagnosis.[10] AIH criteria include serum ALT levels at least five times the upper limit of normal values, serum IgG levels at least two times the upper limit of normal values or a positive test for anti-smooth muscle antibodies, and a liver biopsy showing moderate or severe periportal or periseptal lymphocytic interface necrosis. Meanwhile, PBC criteria consist of serum alkaline phosphatase levels at least two times the upper limit of normal values or serum γ-glutamyl transpeptidase levels at least five times the upper limit of normal values, a positive test for antimitochondrial antibodies, and a liver biopsy showing florid bile duct lesions. Patients who showed several but not all features of AIH-PBC overlap syndrome were categorised as suspicious for overlap syndrome.

Statistical analysis

Fisher's exact test was utilised to analyse the correlation between fibrosis and inflammation progression and the correlation between these histological findings with the trend of aminotransferase levels. Mean ± standard deviation and frequency (percentage) are shown for continuous and categorical data, respectively.

RESULTS

Patient characteristics and indications for liver biopsies

Eighty percent of our patients were female (16 women and 4 men) with an average age of 58.7 ± 12.4 years at the time of repeat liver biopsies. Antinuclear antibody (ANA) was positive in 60% of the patients. Meanwhile, half of the patients were positive for anti-smooth muscle antibody (ASMA). Serum IgG levels were elevated in 60% of patients with available information (9 of 15 patients). The average interval between baseline and repeat biopsies was 6.1 ± 4.6 years.

Based on the IAIHG histological criteria, the baseline liver biopsies of half of our patients were compatible with AIH (50%). Meanwhile, biopsies from seven patients (35%) were typical of AIH and three patients (15%) had atypical biopsies (one patient with overlap AIH-PBC syndrome, one suspicious for AIH-PBC overlap syndrome, and another with a biopsy showing only mild portal lymphocytic infiltrates). Seventeen patients (85%) received immunosuppressive therapy after being diagnosed with AIH, while two patients whose biopsies showed PBC features received ursodeoxycholic acid, and no treatment was given to the patient with non-specific histological finding of mild portal inflammation.

The majority of our patients underwent repeat biopsies because of increased liver function tests and treatment related indications. Eight patients (40%) had elevated aminotransferase levels, while the clinicians performed repeat liver biopsies in eight other patients (40%) before stopping or adjusting the dose of immunosuppressive therapy. In addition, three patients (15%) underwent repeat biopsy for diagnostic clarification and biopsy was performed in another patient (5%) to restage the hepatic fibrosis.

Inflammatory and fibrosis progression does not correlate with the trend of aminotransferase levels

The majority of the patients (60%) showed improved inflammation in the repeat liver biopsies, while five patients (25%) showed similar degree of inflammation, and only three patients (15%) showed worsening of inflammation. There was no significant correlation between inflammatory activities and fibrosis progression ($p = 1.000$). Progressive fibrosis was seen in seven patients (35%), fibrosis was stable in seven other patients (35%), and biopsies from six patients (30%) showed fibrosis regression.

Aminotransferase level information was available from 17 patients (85%). Aminotransferase level testing for three patients was performed at outside hospitals and the information was not available for evaluation. Twelve of seventeen patients (70.6%) showed improvement of aminotransferase levels, and five patients (29.4%) showed worsening aminotransferase levels. The worsening aminotransferase levels did not correlate with the inflammatory activities ($p = 1.000$) and fibrosis progression ($p = 0.116$). Patient characteristics, aminotransferase level trend, and histological information are summarised in Table 1.

Comorbidities are frequently seen in repeat liver biopsies

Eight of 20 patients (40%) showed unexpected histological findings or comorbidities in the repeat liver biopsies. In three patients (15%), steatohepatitis (Fig. 1) was found in the repeat biopsies and biopsies from five patients (25%) showed histological features of cholangiopathy/PBC. Steatohepatitis in the study was defined as steatotic liver with associated inflammation, ballooning degeneration, and pericellular or pericentral fibrosis. None of the patients who developed steatohepatitis had other risk factors per medical records (metabolic syndrome, obesity, alcohol). One patient developed autoimmune cholangitis, and non-specific epithelioid granulomas were seen in repeat liver biopsy of another