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A Retrospective Review of the Diagnostic Rate of Liver Biopsy in Abnormal Liver Tests with Non-Diagnostic Serology and Biochemistry

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Abstract

Abnormal liver function tests, defined as values greater than 2 standard deviations above the upper limits of normal, are noted to be present in up to 7.9% of the population in the United States. In about 69% of patients, they are unexplained by current standard serology or biochemistry markers investigating common viral, autoimmune, hereditary etiologies or inborn errors of metabolism [1, 2].Liver biopsy is considered the most accurate means of grading and staging of liver disease. However, there remains some controversy over whether or not it provides overall significant information in terms of establishing an etiology which would then be used to tailor patient management. [3] Moreover, there is the established possibility of sampling error and accompanying procedure complications during liver biopsy, albeit small [3, 4].

A number of studies have suggested that a high percentage of marker negative liver biopsies had fatty infiltration of the liver with varying degrees of inflammation, with mixed reports on whether there is an association with elements of the metabolic syndrome (obesity, diabetes, dyslipidemia) and improvement with reversal of this syndrome [5, 6, 7, 8]. Several other studies have also reported significant progressive liver disease and even cirrhosis in otherwise asymptomatic patients, who were biopsied with seemingly minor chronic elevations of liver enzymes. These findings subsequently significantly impacted the patient's care [6, 9,10]. However, these were older studies where some biochemical markers were not excluded, and had conflicting conclusions with regards to the diagnostic rate of liver biopsies. [6, 8].

With rapidly advancing imaging technology and biochemical laboratory techniques, the current study seeks to re-evaluate the utility of liver biopsy. Specifically in patients with abnormal liver tests who have had non-diagnostic biochemical or radiographic workup, the rate at which liver biopsy provides a specific diagnosis that can lead to a change to management will be studied.

Keywords: Liver biopsy; Metabolic syndrome; Fatty liver disease;

Methods

A retrospective review of all electronic medical records available and accessible at NorthShore University Hospital and the Long Island Jewish Medical Center in New York was performed. The study was approved by the institutional review board of Northwell Health System. All liver biopsy reports performed from January 1st, 2010 to December 31st, 2015 were obtained and reviewed from the pathology department. The medical records of the respective patients, both inpatient and from the ambulatory setting were reviewed. Subjects were included if they were 18 years of age or older at the time of the liver biopsy, obtained either via percutaneous or trans-jugular approach.

The patients must have already undergone non-diagnostic radiographic testing in the form of either ultrasound, computed tomography, and/or magnetic resonance imaging. A comprehensive biochemical workup must also have been done prior to the biopsy, including viral hepatitis, autoimmune and cholestatic diseases, as well as disorders of iron and copper. The appropriate negative markers were for viral infections (hepatitis A, B, and C, Epstein-barr virus, cytomegalovirus, herpes virus), autoimmune hepatitis (anti-smooth muscle antibody, soluble liver antibody, anti-liver kidney muscle antibody), ceruloplasmin, ferritin, percent iron saturation, alpha-1 antitrypsin, and immunoglobulin levels when available. Hemochromatosis was suspected with an elevated ferritin and iron saturation greater than 45%. The cut-off for ceruloplasmin was 20 mg/dL or less. Anti-nuclear antibody positivity was not used as inclusion criteria without another concurrent marker for autoimmune hepatitis.

Subjects with a liver biopsy with history of known infectious, hereditary, or autoimmune disease or inborn errors of metabolism, as well as those with known neoplasms or hepatic masses were excluded. Patients who reported or were found to have ingestedhepatotoxic medications or drugs, and had active or chronic alcoholism were excluded. The biopsy reports were

deemed useful in guiding treatment if it demonstrated a specific and diagnostic pathological abnormality, including alcoholic liver disease, non-alcoholic fatty liver disease with steatohepatitis, cirrhosis, granulomatous disease, bile duct injury, viral disease or vascular disorder. The study is descriptive, seeking to calculate the rate at which liver biopsies will yield a diagnosis after unrevealing non-invasive workup.

Results

A total of 1505 patients underwent liver biopsies within the study time period.679 liver biopsies were excluded from the study as they were surgical excision specimens and therefore not performed for abnormal liver tests. Another 774 biopsies had incomplete non-invasive liver workup, or were performed for known lesions seen during surgery or on imaging. Fifty-two liver biopsies met inclusion criteria. The male and female ratio was 1:1, comprising of 26 (50%) each (Table 1). Mean age was 54.5±16 years. Caucasian race made up the largest group of patients. The average AST was 167.1±251.1 U/L, ALT 178.3±196.4 U/L, ALP 277.5±333.8 U/L, total bilirubin 3.3±5.8.

Table 1: Basic demographics

Demographics	
Male	26 (50%)
Mean age (years)	54.5±16
BMI (kg/m2)	29.1±7.3
Race	
Caucasian	25 (48%)
Hispanic	8 (15.4%)
African American	4 (7.7%)
Asian	4 (5.8%)
Native American	1 (1.9%)
Other/Multi-racial	4 (7.7%)
Unspecified race	7 (13.5%)

Table 2: Laboratory values

Laboratory Values	
Mean AST (U/L)	167.1±251.1
Mean ALT (U/L)	178.3±196.4
Mean ALP (U/L)	277.5±333.8
Total Bilirubin (mg/dL)	3.3±5.8

Twenty-six (50%) of biopsy reports noted a microscopic description of hepatitis with no clear etiology and did not provide any useful information in guiding patient treatment (Figure 1). Nine of these 26 patients had steatosis without steatohepatitis (NASH). Ten (19.2%) of the 52 patients had histologically confirmed steatohepatitis, all being overweight or obese with an average BMI of 39. Six of the 10 had increased echogenicity on imaging suggestive of steatosis. Aside from the patients with NASH, there were 6 subjects with bile duct injury, 3 malignancies, 2 secondary hemochromatosis, 3 granulomas, 1 of mastocytosis, and 1 congestive hepatopathy. There were 2 patients who were diagnosed with cirrhosis on biopsy that was not suggested by imaging. Overall, 26 (50%) of all the liver biopsies provided a diagnosis and thus guidance in medical management. No instances of bleeding, infection, visceral injury, or complications were reported to arise from the liver biopsies performed.

Discussion

Our study showed that liver biopsy is likely to be informative in patients with abnormal liver blood tests and inconclusive laboratory and radiographic testing. Even with increasingly higher resolutions of radiographic imaging and more sensitive laboratory assays, an etiology is still unknown in a portion of patients with abnormal liver tests. Although liver biopsy is invasive and has an inherent limitation of sampling error, pathological diagnoses have impact on half of our study patients.

Despite the high prevalence of fatty liver disease in the US population [11], those with biopsy proven NASH contributed a small percentage of our subjects. It is therefore incorrect to assume that those with abnormal liver tests and negative non-invasive workup would have NASH and to forgo further workup. Doing so will miss an identifiable cause of their elevated liver enzymes by as much as 50%. All of these patients were at least overweight and had a very high average BMI as expected, given the high correlation between obesity and fatty liver disease. Only a small percentage of the patients with NASH had steatosis on imaging, reaffirming that NASH is definitely a pathologic diagnosis.

Limitations of the study include the inherent selection biases from its retrospective nature. The liver biopsies and pathology reports were not performed by the same physician or pathologist, potentially giving rise to discrepancies between specimens. The liver biopsies with associated incomplete non-invasive workup were excluded. Whether this is due to missing chart information or clinical reasons not evident from the patient's charts, this could have also biased specific etiologies for liver disease and ultimately our results. It is also plausible that patients deemed to have fatty liver disease without steatohepatitis by their physicians would not have been referred for liver biopsy, underestimating patients with NAFLD. The retrospective and comprehensive nature of this study however provides information on the scale of the relatively small number of patients who undergo liver biopsies for abnormal liver tests as well as current practices among physicians at our institution.

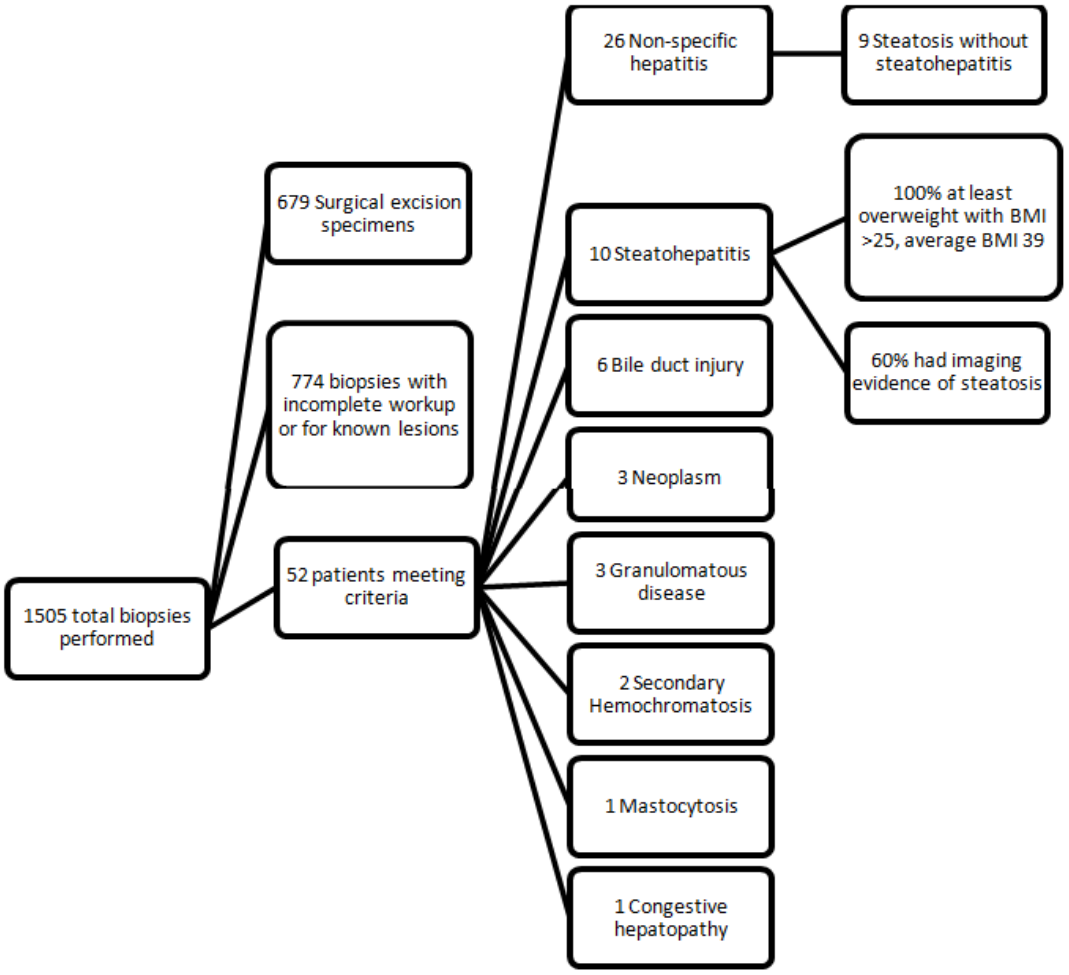

Figure 1: Summary of diagnostic findings from liver biopsies of patients who met inclusion criteria.f

After a careful non-invasive serologic and radiographic workup, liver biopsy is potentially a useful tool in diagnosis and treatment. The valuable diagnostic information obtained can potentially lead to treatment and prevention of worsening liver disease and cirrhosis. Clinicians need to be cognizant of the potentially favorable role of liver biopsy in the evaluation of patients with abnormal liver enzymes.

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