Published in final edited form as:

Dig Dis Sci. 2016 September ; 61(9): 2710–2720. doi:10.1007/s10620-016-4213-3.

Natural History of Patients Presenting with Autoimmune Hepatitis and Coincident Nonalcoholic Fatty Liver Disease

Javier De Luca-Johnson¹, Kirk J. Wangenstein^{2,4}, Joshua Hanson³, Edward Krawitt⁴, and Rebecca Wilcox¹

¹Department of Pathology and Laboratory Medicine, University of Vermont Medical Center, 89 Beaumont Avenue, Courtyard at Given S269, Burlington, VT 05405, USA

²Division of Gastroenterology, Department of Medicine, University of Pennsylvania, 3400 Civic Center Blvd, Philadelphia, PA 19104, USA

³Department of Pathology, University of New Mexico, Reginald Heber Fitz Hall, Room 335, 915 Camino de Salud, Albuquerque, NM 87131, USA

⁴Department of Medicine, University of Vermont Medical Center, 111 Colchester Avenue, Fletcher 311, Burlington, VT 05401, USA

Abstract

Background—Given the increase of nonalcoholic fatty liver disease (NAFLD) in the general population, a similar rise might be expected in autoimmune hepatitis (AIH) patients.

Aims—We sought to determine the clinical outcome of patients with coincident AIH and NAFLD.

Methods—We identified all intradepartmental AIH cases, and those meeting study criteria were placed into one of three cohorts: AIH only, AIH and simple steatosis (SS), and AIH and nonalcoholic steatohepatitis (NASH). The following outcome and clinical data were analyzed: incidence of all-cause mortality, incidence of liver-related mortality, incidence of liver-related adverse outcomes, and prevalence of cirrhosis at index biopsy.

Results—Out of a total 73 study patients, 14 % classified as AIH with SS and 16 % as AIH and NASH. Fifty percent of AIH and NASH patients had cirrhosis at index biopsy as compared to 18 % of AIH-only patients ($p = 0.032$). Patients with AIH and NASH had a relative risk of 7.65 (95 % CI 1.43–40.8) for liver-related mortality and 2.55 (95 % CI 0.92–7.09) for liver-related adverse outcomes, as compared to the AIH-only cohort. No significant difference in outcome measures existed in comparing (AIH only) with (AIH and SS) cohorts.

Discussion—Patients with coincident AIH and NASH were more likely to present with cirrhosis and more likely to develop adverse clinical outcome with decreased survival as compared to AIH-only patients. These findings suggest that simultaneous exposure confers a clinically significant increased risk, which may warrant closer follow-up and surveillance.

✉ Javier De Luca-Johnson, Javier.DeLuca-Johnson@uvmhealth.org.

Conflict of interest The authors disclose no conflicts and/or financial support.

Keywords

Autoimmune hepatitis; Nonalcoholic steatohepatitis; Nonalcoholic fatty liver disease; Diabetes mellitus; Obesity

Introduction

Due to the rising levels of diabetes and obesity and the emerging “epidemic” of the metabolic syndrome, the burden of nonalcoholic fatty liver disease (NAFLD) in the general population continues to grow [1–4]. NAFLD has become prevalent to the point where it is now the most common liver disorder in the USA, with current estimates of NAFLD prevalence ranging from 20 to 35 %.

The rising prevalence of NAFLD in the general population carries important diagnostic, therapeutic, and long-term clinical management implications for patients with other kinds of chronic liver disease. As the prevalence of NAFLD in the general population continues to rise, we may expect to see more and more coincidental NAFLD in patients with chronic liver diseases such as chronic viral hepatitis, alcoholic hepatitis, hemochromatosis, alpha-1 antitrypsin deficiency, primary biliary cholangitis, or autoimmune hepatitis (AIH) [5–8]. This is of clinical concern, as patients who are exposed to two chronic liver diseases may have a worse clinical outcome and worse survival as compared to patients with a single chronic liver disease.

The presence of NAFLD in patients with AIH remains a poorly characterized and rarely described clinical entity. To our knowledge, only 16 cases of AIH-NAFLD co-occurrence have been reported in the literature, and of those, only 8 cases represent AIH co-occurrence with nonalcoholic steatohepatitis (NASH), the more clinicopathologically advanced form of NAFLD [5, 9–13]. Co-occurrence of AIH and NAFLD is important from a diagnostic standpoint because autoantibodies are known to occur with increased prevalence in patients with NAFLD, as compared to the prevalence of autoantibodies in the general population [9–15]. This so-called non-organ specific autoimmunity occurs in the absence of traditional autoimmune disease, making the detection and diagnosis of true autoimmune conditions such as AIH challenging. Therapeutically, it is important to accurately recognize NAFLD in AIH because the standard treatment for AIH, glucocorticoids, could potentially worsen NAFLD. Finally, the clinical outcome and prognostic significance of incidental AIH and NAFLD have yet to be characterized.

We performed a retrospective cohort study with the goal of characterizing the diagnostic, histologic, and therapeutic features and long-term clinical outcome of patients with both AIH and NAFLD as compared to AIH patients without NAFLD.

Materials and Methods

The study protocol was approved by the University of Vermont Medical Center Institutional Review Board (IRB#CHRMS12-213). As a retrospective cohort study with minimal risk to

the individual, the University of Vermont Medical Center Institutional Review Board approved a waiver for informed consent applicable to all study patients.

Subjects

The clinicopathologic records, index biopsy, and follow-up biopsies of patients with type 1 autoimmune hepatitis accessioned at the Department of Pathology, University of Vermont, in the years 1973–2011 were reviewed. Patient medical charts were surveyed for age, gender, comorbidities (type I or II diabetes mellitus, body mass index (BMI), hyperlipidemia, hypertension), history of alcohol use, presenting symptoms, treatment data, and long-term clinical and histologic outcome data (liver-related and all-cause mortality, liver-related adverse outcomes, and follow-up liver biopsies). Of those patients who received treatment following index biopsy, complete response to treatment was defined as either follow-up biopsy with grade 0 inflammation (histologic response) or normalization of transaminases up to 2 years after having started therapy (biochemical response). The following AIH-specific laboratory data were collected: autoimmune serologies, IgG or globulin levels, and hepatitis B and C serologies. In all patients whose index liver biopsy had been obtained prior to the discovery of the hepatitis C virus, subsequent testing for the virus was performed and documented.

Histologic Review

For identified AIH patients with available clinical data, all index biopsies were histologically reviewed. We used the simplified criteria for the diagnosis of autoimmune hepatitis (SCAIH), as defined by the International Autoimmune Hepatitis Group (IAIHG) in 2008, to classify the histologic features of AIH as “atypical histology” (0 points), “histology compatible with AIH” (1 point), or “typical histology” (2 points) [16]. Grade and stage were assigned according to Batts–Ludwig classification [17, 18]. The presence or absence of steatosis or steatohepatitis was recorded together with an estimation of severity. When steatohepatitis was present, the characteristics were recorded according to the modified Brunt system: acute lobular hepatitis (polymorphonuclear), ballooning degeneration of hepatocytes, and pericellular/perisinusoidal fibrosis [19, 20].

Inclusion and Exclusion Criteria

The clinical and laboratory data at the time of the index biopsy were combined with the results of the histologic review. Inclusion in the study required a SCAIH score ≥ 6 . Exclusion criteria were heavy alcohol use (>21 drinks/week for men and >14 drinks/week for women), positive titers for hepatitis B and/or C, prior liver transplant, and SCAIH score ≥ 6 based on clinical criteria without histologic features of AIH.

Retrospective Cohort Outcomes Analysis

All cases of concurrent AIH and NAFLD were identified, and NAFLD cases were further subdivided into simple steatosis (SS) and NASH. Patients were placed into one of three cohorts (AIH, AIH and SS, and AIH and NASH). The following outcome and clinical data among the three cohorts were analyzed: incidence of all-cause mortality, incidence of liver-related mortality, incidence of liver-related adverse outcome, and prevalence of cirrhosis at

the time of index biopsy. Adverse outcome was defined as development of cirrhosis on a biopsy sample, hepatocellular carcinoma (HCC), portal hypertension, ascites, or hepatic encephalopathy. Liver-related mortality was defined as death with a primary cause of complications of cirrhosis and/or hepatocellular carcinoma.

The following histologic outcome data were captured for all three cohorts: time interval to follow-up biopsy (or biopsies) and grade and stage of liver disease. The delta of the grade and the stage were calculated as the grade or stage on first follow-up biopsy minus the grade or stage on index biopsy, respectively.

Statistical Analysis

Statistical analysis was performed on SPSS statistical software package (version 22 for Windows; SPSS Inc, Chicago, IL). Categorical data are presented as number (%). Continuous data are presented as mean (SD). Fisher's exact and Chi-squared tests were performed to compare discrete and categorical data, respectively. Separate two-sided *p* values were calculated for the following comparisons: AIH versus AIH and SS and AIH versus AIH and NASH.

Incidence rate was defined as the number of total events among a cohort, divided by the cumulative follow-up time, multiplied by one hundred. Relative risk and 95 % confidence intervals were calculated from the incidence rates of cohorts that were being compared: AIH versus AIH and SS and AIH versus AIH and NASH. To control for age-related confounding, secondary outcome analysis was performed with exclusion of patients in the second and third decades of life. Follow-up time was defined as the time in years from index biopsy until death or until the end of the study period (2012) in person-years. Several patients were lost to follow-up. In these cases, follow-up time was defined as the time from index biopsy until the time of the last internal medicine or gastroenterology/hepatology clinic note.

Results

Study Population and Prevalence of NALFD

Of the 127 identified AIH index biopsies, 73 met study selection criteria for AIH (Fig. 1). Thirty percent (22/73) of patients with AIH demonstrated coincident NAFLD. Specifically, 14 % (10/73) had simple steatosis and 16 % (12/73) had NASH (Figs. 2, 3, 4).

Clinical Parameters

Overall, the age ranged from 11 to 78, with mean age of 50 (SD 17; Table 1). Age distribution demonstrated bimodal pattern, with a large peak in the fifth through seventh decades and a smaller peak clustered in the second decade. Patients presenting at a young age (age < 30) were all in the AIH cohort. There was an overall female predominance (45 of 73, or 62 %). There was no statistically significant difference in age or gender among the cohorts. The year of index biopsy ranged widely from 1976 to 2011; however, the great majority (93 %) of cases were from the 1990s to the present. The year of index biopsy for patients in the AIH and SS cohort was significantly later than in the AIH cohort (*p* = 0.039). The presence of NASH was significantly associated with diabetes mellitus type II (*p* =

0.027), hyperlipidemia ($p = 0.008$), and hypertension ($p = 0.037$). The presence of simple steatosis was significantly associated with obesity ($p = 0.020$) and hypertension ($p = 0.008$).

Nearly two-thirds of all patients received treatment following index biopsy (48 out of 73, or 66 %; Table 2). A small subset of patients initiated treatment prior to the index biopsy (4 out of 73, or 5 %); these patients were relatively well distributed across cohorts (1 AIH patient, 2 AIH and SS patient, and 1 AIH and NASH patient). Two patients (3 % of total) did not receive treatment after the index biopsy but were eventually started on therapy based on the findings of a subsequent follow-up biopsy. In all, 12 patients (16 %) received no treatment at any point during the study period. Reasons for non-treatment included spontaneous remission ($N = 1$), autoimmune overlap syndrome ($N = 3$), and cryptogenic cirrhosis ($N = 4$). Of patients who were treated, slightly less than half received monotherapy with prednisone or less commonly budesonide (24 out of 54, or 44 %). Twenty patients (37 %) were treated with dual or multidrug therapy with a glucocorticoid plus a non-glucocorticoid agent such as 6-mercaptopurine, azathioprine, methotrexate, or mycophenolate mofetil. Ten patients (19 %) were treated exclusively with non-glucocorticoid therapy. There was no statistically significant difference between cohorts when comparing history of treatment or mode of treatment.

Of those patients who received treatment following index biopsy, 38 (79 %) had clinical and/or histologic response data available. Overall, 28 of those patients (74 %) demonstrated complete biochemical and/or histologic response. Response rates across cohorts ranged from 71 % response rate in the AIH cohort to 80 % response rates in the AIH and SS and AIH and NASH cohorts. There was no statistically significant difference between cohorts when comparing response rates.

Histologic Features

The overall mean (SD) grade and stage of fibrosis at time of diagnosis was 2.5 (0.73) and 2.7 (0.90), respectively (Table 3).

Patients with AIH and NASH were more likely to present with histologic features “compatible with AIH” (1 point) rather than “typical for AIH” (2 points; $p = 0.018$) and were more likely to present at a lower grade ($p = 0.050$) as compared to patients in the AIH cohort. There was no significant difference in the mean fibrosis stage for the AIH and NASH cohort; however, when analyzed stage-for-stage, 50 % of NASH patients had cirrhosis at time of index biopsy (stage 4) as compared to 18 % of AIH-only patients ($p = 0.032$). Biopsy findings in the AIH and SS were equivalent to the AIH cohort with none of the histologic parameters achieving statistical significance. Patients in the AIH and NASH cohort had a higher mean percent steatosis (36 %) when compared to the AIH and SS cohort (24 %; $p = 0.0080$).

Outcomes Analysis: Clinical Parameters

Patients in the AIH and NASH cohort had significantly increased incidence of adverse events with a statistically significant or near statically significant relative risk of liver-related mortality, all-cause mortality, and liver-related adverse outcomes (Tables 4, 5). For example, during the follow-up period, 25 % (3/12) of patients with AIH and NASH died from liver-

related causes as compared to only 4 % (2/51) of AIH patients, with an incidence rate of 3.26 for the AIH and NASH cohort versus 0.426 in the AIH cohort (RR 7.65; 95 % CI 1.43–40.8). For all-cause mortality, 42 % (5/12) in the AIH and NASH cohort died as compared to 22 % (11/51) of AIH patients, with an incidence rate of 5.43 for the AIH and NASH cohort versus 2.35 for the AIH cohort (RR 2.32; 95 % CI 0.991–5.42). Finally, liver-related adverse outcome occurred in 33 % (4/12) of AIH and NASH patients as compared to 16 % (8/51) of AIH patients, with an incidence rate of 4.35 in the AIH and NASH cohort versus 1.71 in the AIH cohort (RR 2.55; 95 % CI 0.92–7.09). There was no significant difference in outcome measures when comparing AIH patients to patients with AIH and SS.

The AIH and NASH cohort was on average 10 years older than the AIH cohort (58 vs. 48 years), although this difference did not achieve statistical significance (Table 1). Patients in the second and third decade of life were found only in the AIH cohort and were excluded for secondary clinical outcomes analysis (Table 4). Exclusion of younger patients increased the average age of the AIH cohort to 55 (range 31–75 years, SD 12). Relative risk across all clinical outcome measures decreased following secondary analysis; however, relative risk of liver-related death remained statistically significant (RR 6.49; 95 % CI 1.22–34.6).

Outcomes Analysis: Histologic Parameters

Follow-up biopsy was available for 34 % of patients (25/73), with the majority belonging to the AIH cohort (18/25). The time to first follow-up biopsy averaged 5.0 years (range 1–17 years, SD 6). When measured to the last follow-up biopsy, the average follow-up time was 7.4 years (range 1–30 years, SD 6.8). There was no statistically significant difference in follow-up time among the three cohorts, regardless of whether follow-up time was measured to the first or the last follow-up biopsy.

Overall, necroinflammatory grade tended to decrease on follow-up biopsy (mean delta grade -1.2 , range -3 to 1.5 , SD -1.0). The delta grade was not statistically significant when compared across the three cohorts. The overall delta stage averaged near zero (mean delta stage -0.02 , range -2 to 2 , SD 0.58). Delta stage was higher in the AIH and SS cohort (mean 1.2 , range 0 – 2 , SD 1.0) versus the AIH cohort (mean -0.22 , range -2 to 2 , SD 1.3 ; $p = 0.03$); however, the sample size for the AIH and SS cohort was very small ($N = 3$). Delta stage was not statistically significant when comparing the AIH and NASH cohort to the AIH cohort. Of note, 50 % of AIH and NASH patients presented with stage 4 at index biopsy (Table 3), leaving little room for stage progression.

Seventy-six percent of patients with follow-up biopsies (19/25) received treatment following index biopsy (Table 6). Across all cohorts, patients who did not receive treatment had a higher delta grade (mean 0.42 , SD 0.92) as compared to those patients did receive treatment (mean -1.71 , SD 0.90 ; $p < 0.0005$). Delta stage for those who did not receive treatment was higher (mean 0.58 , SD 0.92) than for those who did receive treatment (mean -0.21 , SD 0.92); however, this parameter did not achieve statistical significance ($p = 0.08$).

Discussion

This study represents the largest report to date on the diagnostic and therapeutic features and the long-term clinical outcome of patients with coincident AIH and NAFLD. Previously published reports were limited to at most four cases with both AIH and NAFLD, with limited reported therapeutic, histologic and outcome data. Additionally, these previous reports looked exclusively at the prevalence of AIH in a cohort of NAFLD patients, while our study takes the inverse approach, i.e., examining the prevalence of NAFLD in AIH patients.

The major finding of this study is that patients with AIH who were exposed to metabolic damage in the form of NASH were more likely to present with cirrhosis and were more likely to have decreased survival due to liver-related death as compared to AIH patients who did not have NASH. The finding of liver-related death remained significant after modifying the analysis to account for age differences among the cohorts. Similar trends were seen for all-cause mortality and non-fatal liver-related adverse outcome; however, these comparisons did not achieve statistical significance. Although the absolute number of adverse events was low, the AIH and NASH cohort had a disproportionately higher rate of adverse events, suggesting that coincident NASH accelerates the rate of liver damage from AIH. In contrast to the clinical outcome data, the data for histologic changes over time for the AIH and NASH cohort were not different than for the AIH cohort, though our sample size for follow-up biopsies was small.

Patients with uncomplicated steatosis (simple steatosis) did not show any difference in clinical outcome. This suggests that fatty liver disease needs to progress to the more advanced clinicopathologic state of steatohepatitis before physiologic damage becomes significant enough to affect the long-term outcome.

Remarkably, the prevalence of NASH among our cohort of AIH patients (16 %) was higher than the estimated prevalence in the general population, where it has been estimated to be between 3 and 5 % [1, 2]. Furthermore, in our study population the number of NASH cases outnumbered the cases with simple steatosis. The higher prevalence of NASH may be indicative of the increased physiologic burden of having two chronic liver diseases, in that patients with two chronic liver diseases such as AIH and NAFLD may have an increased rate of progression from uncomplicated steatosis to steatohepatitis.

In contrast to NASH prevalence, the overall prevalence of NAFLD in our study population (30 %) closely matches the prevalence data for the general population (estimated at 20–35 %) [1, 2]. Additionally, most of the metabolic syndrome risk factors we analyzed (diabetes mellitus, obesity, hypertension, hyperlipidemia) were significantly associated with both the SS and NASH cohorts. These findings (metabolic syndrome association and a prevalence which is equal to that of the general population) support a coincidental, and not causal, association between NAFLD and AIH.

Co-occurrence of AIH and NAFLD presents several diagnostic and therapeutic challenges. Diagnostically, there is both clinical and histologic overlap that can affect the ability to accurately diagnose the presence of both AIH and NAFLD (especially NASH) in the same

patient. Clinically, the high prevalence of non-organ specific autoantibodies in NALFD may drive up the IAHG score, resulting in diagnostic confusion. Multiple studies have demonstrated that based on clinical criteria alone, as many as 20 % of NAFLD patients may in fact qualify for a diagnosis of AIH prior to liver biopsy [12]. For this reason, positive histologic findings are mandatory for the diagnosis of AIH as outlined in the IAHG scoring criteria [16]. With regards to histology, AIH and NASH may demonstrate overlapping features. For example, NASH can have portal inflammation. Importantly, the portal inflammation in NASH is primarily lymphocytic with a minimal plasma cell component. Conversely, the histologic features of AIH in the advanced necroinflammatory grades may mimic NASH in that there is extensive lobulitis and parenchymal collapse that notoriously picks up trichrome stain. The histologic overlap may make diagnosis of both disorders on the same biopsy challenging, as evidenced in our current study, where comparison of the study histologic interpretation with the historical surgical pathology report revealed that the diagnosis of NASH was initially missed in 3 of 12 cases in our AIH and NASH cohort (25 %).

Therapeutically, patients who have both AIH and NAFLD present a significant diagnostic dilemma. The standard therapy for AIH is glucocorticoids (usually prednisone, less often budesonide), which could potentially worsen underlying NAFLD. Non-glucocorticoid therapy, such as 6-mercaptopurine, azathioprine, methotrexate, or mycophenolate mofetil, is available and may be less likely to worsen NAFLD. In our study population, the majority of patients (66 %) underwent treatment following the index biopsy, and of all those who were treated, 83 % received glucocorticoid therapy, either singly or in combination with a second non-glucocorticoid agent. There was no statistically significant difference between our NAFLD patients and non-NAFLD patients when looking at history of treatment or treatment modality. Importantly, patients with NAFLD received a similar proportion of glucocorticoid therapy and were not more likely to be treated by alternative non-glucocorticoid measures. An isolated case report demonstrated clinical resolution of both AIH and NASH in a patient treated with prednisone; however, this remains the only case demonstrating proven benefit of prednisone therapy in patients with both AIH and NASH (11). Therefore, the optimal treatment regimen for patients presenting with both AIH and NAFLD is uncertain at this time. Weight loss and exercise have the strongest evidence for improvement of NASH [21]. While weight loss would seem like a reasonable recommendation for patients with AIH and NASH who are overweight, further study is needed.

This study has several limitations. Lack of available clinical data, especially for those cases originating prior to the year 2000, resulted in the exclusion of several study cases despite the demonstration of convincing histologic features of AIH on microscopic review. While the AIH cohort ($N=51$) was of a relatively robust size, the smaller sizes of our AIH and SS cohort ($N=10$) and the AIH and NASH cohort ($N=12$) limited our ability to perform certain kinds of statistical outcome analysis (Kaplan–Meier survival curves) and multivariate analysis. With a larger cohort of SS and NASH patients, it would be especially informative to report outcome measures after controlling for variables such as history of treatment and/or history of glucocorticoid-specific therapy. Another major limitation was that a substantial number of cases lacked clinical documentation of the cause of death. In those cases, patients were determined to have died of all-cause rather than of liver-related mortality. However,

this may have underestimated the overall number of liver-related deaths, especially in the AIH cohort.

In summary, we performed a retrospective cohort study with the goal of characterizing the diagnostic, histologic, and therapeutic features and long-term clinical outcome of patients with coincident AIH and NAFLD as compared to AIH patients without NAFLD. The findings suggest that simultaneous exposure to two chronic liver diseases confers a clinically significant increased level of risk and may warrant closer follow-up and surveillance. Additionally, we found that patients with AIH and uncomplicated steatosis were at no greater risk of adverse outcomes, suggesting that fatty liver disease must progress to a more advanced clinicopathologic state of steatohepatitis before physiologic damage becomes significant enough to alter the long-term outcome.

Acknowledgments

Preliminary histologic findings were reported as a platform presentation at the 2013 annual meeting of the United States and Canadian Academy of Pathology (Baltimore, MD, March 4, 2013). Clinical outcome data were reported as a poster presentation at the 2015 annual meeting of the United States and Canadian Academy of Pathology (Boston, MA, March 25, 2015).

References

1. Masuoka HC, Chalasani N. Nonalcoholic fatty liver disease: an emerging threat to obese and diabetic individuals. *Ann NY Acad Sci* 2013;1281:106–122. [PubMed: 23363012]
2. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment Pharmacol Ther* 2011;34:274–285. [PubMed: 21623852]
3. Bedogni G, Nobili V, Tribelli C. Epidemiology of fatty liver: an update. *World J Gastroenterol* 2014;20:9050–9054. [PubMed: 25083078]
4. Williams CD, Stengel J, Asike MI, et al. Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and liver biopsy: a prospective study. *Gastroenterology*. 2011;140:124–131. [PubMed: 20858492]
5. Brunt EM, Ramrakhiani S, Cordes BG, et al. Concurrence of histologic features of steatohepatitis with other forms of chronic liver disease. *Mod Pathol* 2003;16:49–56. [PubMed: 12527713]
6. Yoon H, Lee JG, Yoo JH, et al. Effects of metabolic syndrome on fibrosis in chronic viral hepatitis. *Gut Liver*. 2013;7:469–474. [PubMed: 23898389]
7. Sanyal AJ, Contos MJ, Sterling RK, et al. Nonalcoholic fatty liver disease in patients with hepatitis C is associated with features of the metabolic syndrome. *Am J Gastroenterol*. 2003;98:2064–2071. [PubMed: 14499789]
8. Bedossa P, Moucari R, Chelbi E, et al. Evidence for a role of nonalcoholic steatohepatitis in hepatitis C: a prospective study. *Hepatology*. 2007;46:380–387. [PubMed: 17659580]
9. Loria P, Lonardo A, Leonardi F, et al. Non-organ specific autoantibodies in nonalcoholic fatty liver disease: prevalence and correlates. *Dig Dis Sci* 2003;48:2173–2181. [PubMed: 14705824]
10. Cotler S, Kanji K, Keshavarzian A, Jensen DM, Jakate S. Prevalence and significance of autoantibodies in patients with non-alcoholic steatohepatitis. *J Clin Gastroenterol* 2004;38:801–804. [PubMed: 15365409]
11. Fukuda S, Komori A, Itoh M, et al. Histological remission during corticosteroid therapy of overlapping nonalcoholic steatohepatitis and autoimmune hepatitis: case report and literature review. *Case Rep Gastroenterol* 2011;5:553–557. [PubMed: 22110414]
12. Adams LA, Lindor KD, Angulo P. The prevalence of autoantibodies and autoimmune hepatitis in patients with nonalcoholic fatty liver disease. *Am J Gastroenterol* 2004;99:1316–1320. [PubMed: 15233671]

13. Yatsuji S, Hashimoto E, Kaneda H, Taniai M, Tokushige K, Shiratori K. Diagnosing autoimmune hepatitis in nonalcoholic fatty liver disease: is the International Autoimmune Hepatitis Group scoring system useful? *J Gastroenterol*. 2005;40:1130–1138. [PubMed: 16378177]
14. Niwa H, Sasaki M, Haratake J, et al. Clinicopathological significance of antinuclear antibodies in non-alcoholic steatohepatitis. *Hepatol Res* 2007;37:923–931. [PubMed: 17610500]
15. Vuppalanchi R, Gould RJ, Wilson LA, et al. Clinical significance of serum autoantibodies in patients with NAFLD: results from the nonalcoholic steatohepatitis clinical research network. *Hepatol Int* 2012;6:379–385. [PubMed: 21557024]
16. Hennes EM, Zeniya M, Czaja AJ, et al. Simplified criteria for the diagnosis of autoimmune hepatitis. *Hepatology*. 2008;48:169–176. [PubMed: 18537184]
17. Batts KP, Ludwig J. Chronic hepatitis. An update on terminology and reporting. *Am J Surg Pathol* 1995;19:1409–1417. [PubMed: 7503362]
18. Batts KP, Ludwig J. Histopathology of autoimmune hepatitis, primary biliary cirrhosis and primary sclerosing cholangitis In: Krawitt EL, Wiesner RH, Nishioka M, eds. *Autoimmune Liver Diseases*. 2nd ed. Amsterdam: Elsevier; 1998.
19. Brunt EM, Janney CG, Di Bisceglie AM, Neuschwander-Tetri BA, Bacon BR. Nonalcoholic steatohepatitis: a proposal for grading and staging the histological lesions. *Am J Gastroenterol* 1999;94:2467–2474. [PubMed: 10484010]
20. Brunt EM. Pathology of nonalcoholic fatty liver disease. *Nat Rev Gastroenterol Hepatol* 2010;7:195–203. [PubMed: 20195271]
21. Keating SE, Hackett DA, George J, Johnson NA. Exercise and non-alcoholic fatty liver disease: a systematic review and meta-analysis. *J Hepatol* 2012;57:157–166. [PubMed: 22414768]

Fig. 1.

Flowchart demonstrating our retrospective cohort study design. *IAHG* International Autoimmune Hepatitis Group, *NAFLD* nonalcoholic fatty liver disease, *AIH* autoimmune hepatitis, *NASH* nonalcoholic steatohepatitis, *SCAIH* simplified criteria for the diagnosis of autoimmune hepatitis

Fig. 2.
Study patient; index AIH biopsy with superimposed NASH. Histologic features of AIH are present (interface hepatitis with plasma cells at leading edge of inflammation) along with histologic features of NASH (polymorphonuclear inflammatory cells with ballooned hepatocytes; H&E, $\times 100$)

Fig. 3.
Study patient; index AIH biopsy with superimposed NASH. Higher power highlights active steatohepatitis with ballooned hepatocytes (H&E, $\times 200$)

Fig. 4.
Study patient; index AIH biopsy with superimposed NASH. Trichrome stain in same focus demonstrates pericellular/perisinusoidal fibrosis surrounding ballooned hepatocytes (Trichrome, $\times 200$)

Table 1

Overall and cohort-specific clinical and demographic features of the study population

Variable	Overall (N = 73)	AIH (N = 51)	AIH and SS (N = 10)	p value, AIH versus AIH and SS	AIH and NASH (N = 12)	p value, AIH versus AIH and NASH
Age at index biopsy [years, mean (range, SD)]	50 (11–78, 17)	48 (11–75, 19)	54 (33–77, 12)	0.30	58 (38–78, 12)	0.077
Age at index biopsy by decade of life, n (%)						
0–9	0	0	0	–	0	–
10s	6 (8)	6 (12)	0	–	0	–
20s	3 (4)	3 (6)	0	–	0	–
30s	7 (9.5)	5 (10)	1 (10)	–	1 (8)	–
40s	13 (18)	10 (20)	2 (20)	–	1 (8)	–
50s	18 (25)	10 (20)	3 (30)	–	5 (42)	–
60s	19 (26)	13 (25)	3 (30)	–	3 (25)	–
70s	7 (9.5)	4 (8)	1 (10)	–	2 (17)	–
Female gender, n (%)	45 (62)	29 (57)	9 (90)	0.074	7 (58)	1.00
Year of index biopsy, mean (range)	2000 (1976–2011)	2000 (1976–2011)	2006 (1992–2011)	0.039	2001 (1985–2008)	0.77
Year of index biopsy by decade, n (%)						
1970s	2 (3)	2 (4)	0	–	0	–
1980s	3 (4)	2 (4)	0	–	1 (8)	–
1990s	20 (27)	17 (33)	1 (10)	–	2 (17)	–
2000–2011	48 (66)	30 (59)	9 (90)	–	9 (75)	–
Diabetes mellitus, type II, n (%)	12 (16)	6 (12)	1 (10)	0.68	5 (42)	0.027
Diabetes mellitus, type I, n (%)	0	0	0	–	0	–
Obesity, n (%)	24 (33)	12 (24)	7 (70)	0.020	5 (42)	0.31
Hypertension, n (%)	33 (45)	17 (33)	8 (80)	0.0080	8 (67)	0.037
Hyperlipidemia, n (%)	20 (27)	9 (18)	4 (40)	0.13	7 (58)	0.0080

Unless otherwise noted, data shown as n (%) for categorical variables and mean (SD) for continuous variables

AIH autoimmune hepatitis, SS simple steatosis, NASH nonalcoholic steatohepatitis

Table 2

Overall and cohort-specific treatment features of the study population

Variable	Overall (N = 73)	AIH (N = 51)	AIH and SS (N = 10)	p value, AIH versus AIH and NASH	AIH and NASH (N = 12)	p value, AIH versus AIH and NASH
Treatment history						
Received treatment prior to index biopsy, <i>n</i> (%)	4 (5)	1 (2)	2 (20)	0.067	1 (8)	0.35
Received treatment due to results of index biopsy, <i>n</i> (%)	48 (66)	37 (73)	5 (50)	0.26	6 (50)	0.17
Received treatment only after a follow-up biopsy, <i>n</i> (%)	2 (3)	0 (0)	1 (10)	0.16	1 (8)	0.19
No treatment received, <i>n</i> (%)	12 (16)	9 (18)	2 (20)	1.00	1 (8)	0.67
Incomplete clinical notes, <i>n</i> (%)	7 (10)	4 (8)	0	1.00	3 (25)	0.081
Treatment modality						
Glucocorticoid therapy ^a , <i>n</i> (%)	24/54 (44)	15/38 (39)	5/8 (62.5)	0.27	4/8 (50)	0.70
Combined glucocorticoid and non-glucocorticoid therapy ^b , <i>n</i> (%)	20/54 (37)	14/38 (37)	3/8 (37.5)	1.00	3/8 (37.5)	1.00
Non-glucocorticoid therapy, <i>n</i> (%)	10/54 (19)	9/38 (24)	0/8 (0)	0.32	1/8 (12.5)	0.66
Treatment response rate						
Biochemical and/or histologic response data available, <i>n</i> (%)	38/48 (79)	28/37 (76)	5/5 (100)	0.57	5/6 (83)	1.00
Complete biochemical and/or histologic response, <i>n</i> (%)	28/38 (74)	20/28 (71)	4/5 (80)	1.00	4/5 (80)	0.23
Reasons for non-treatment						
Spontaneous remission, <i>n</i> (%)	1/12 (8)	1/9 (11)	0/2 (0)	–	0/1 (0)	–
Autoimmune overlap, <i>n</i> (%)	3/12 (25)	2/9 (22)	1/2 (50)	–	0/1 (0)	–
Cryptogenic cirrhosis, <i>n</i> (%)	4/12 (33)	3/9 (33)	0/2 (0)	–	1/1 (100)	–
Incomplete clinical notes, <i>n</i> (%)	4/12 (33)	3/9 (33)	1/2 (50)	–	0/1 (0)	–
Reasons for delayed treatment						
Patient declined treatment, <i>n</i> (%)	1/2 (50)	0	1/1 (100)	–	0/1 (0)	–
Incomplete clinical notes, <i>n</i> (%)	1/2 (50)	0	0/1 (100)	–	1/1 (100)	–

Unless otherwise noted, data shown as *n* (%) for categorical variables and mean (SD) for continuous variables

AIH autoimmune hepatitis, SS simple steatosis, NASH nonalcoholic steatohepatitis

^aGlucocorticoid therapy includes prednisone or budesonide^bNon-glucocorticoid therapy includes 6-mercaptopurine, azathioprine, methotrexate, or mycophenolate mofetil

Table 3

Histologic comparison of AIH cohorts at index biopsy

Variable	Overall (N = 73)	AIH (N = 51)	AIH and SS (N = 10)	p value AIH versus AIH and steatosis	AIH and NASH (N = 12)	p value AIH versus AIH and NASH
AIH histology, n (%)						
Compatible	29 (40)	16 (31)	5 (50)	0.83	8 (67)	0.018
Typical	44 (60)	35 (69)	5 (50)	—	4 (33)	—
Grade, mean (SD)	2.5 (0.73)	2.8 (0.62)	2.2 (0.79)	0.37	2.0 (0.74)	0.050
Grade, n (%)						
Acute	4 (5)	4 (8)	0	—	0	—
0	0	0	0	—	0	—
1	6 (8)	1 (2)	2 (20)	—	3 (25)	—
2	24 (33)	14 (27)	4 (40)	—	6 (50)	—
2.5	1 (1)	1 (2)	0	—	0	—
3	28 (38)	21 (41)	4 (40)	—	3 (25)	—
3.5	10 (14)	10 (20)	0	—	0	—
4	0	0	0	—	0	—
Stage, mean (SD)	2.7 (0.90)	2.7 (0.91)	2.1 (1.20)	0.070	3.1 (0.96)	0.18
Stage, n (%)						
Acute	4 (5)	4 (8)	0	—	0	—
0	2 (3)	1 (2)	1 (10)	—	0	—
1	4 (5)	2 (4)	2 (20)	—	0	—
2	21 (29)	14 (27)	3 (30)	—	4 (33)	—
2.5	5 (7)	4 (8)	0	—	1 (8.3)	—
3	19 (26)	15 (29)	3 (30)	—	1 (8.3)	—
3.5	2 (3)	2 (4)	0	—	0	—
4	16 (22)	9 (18)	1 (10)	1.00	6 (50)	0.032
Steatosis, mean (SD)	—	—	24 % (0.17)	—	36 % (0.18)	0.0080 *
Steatosis, n (%)						
0	24 (33)	24 (47)	0	—	0	—
<5 %	27 (37)	27 (53)	0	—	0	—
1	14 (19)	0	7 (70)	—	7 (58)	—

Variable	Overall (N = 73)	AIH (N = 51)	AIH and SS (N = 10)	p value AIH versus AIH and steatosis	AIH and NASH (N = 12)	p value AIH versus AIH and NASH
2	7 (10)	0	3 (30)	–	4 (33)	–
3	1 (1)	0	0	–	1 (8.3)	–
NASH histology						
Inflammation, <i>n</i> (%)	12 (16)	0 (0)	0 (0)	–	12 (100)	–
Ballooning, <i>n</i> (%)	26 (36)	13 (25)	1 (10)	–	12 (100)	–
Fibrosis, <i>n</i> (%)	30 (41)	18 (35)	1 (10)	–	12 (100)	–

AIH autoimmune hepatitis, SS simple steatosis, NASH nonalcoholic steatohepatitis

*The calculated *p* value is for AIH and NASH versus AIH and SS comparison

Table 4

Comparison of long-term clinical outcome among cohorts (incidence data)

Outcome variable	AIH cohort (N = 51)			AIH and NASH cohort (N = 12)			Relative risk (95 % CI)
	Cases, <i>n</i> (%)	Cumulative person-years	Incidence rate (events/person-years × 100)	Cases, <i>n</i> (%)	Cumulative person-years	Incidence rate (events/person-years × 100)	
Comparison: entire cohort							
Liver-related death	2/51 (4)	469	0.426	3/12 (25)	92	3.26	7.65 (1.43–40.8)
All-cause death	11/51 (22)		2.35	5/12 (42)		5.43	2.32 (0.991–5.42)
Liver-related adverse outcome	8/51 (16)		1.71	4/12 (33)		4.35	2.55 (0.92–7.09)
Outcome variable	AIH cohort (N = 42)			AIH and NASH cohort (N = 12)			Relative risk (95 % CI)
	Cases, <i>n</i> (%)	Cumulative person-years	Incidence rate (events/person-years × 100)	Cases, <i>n</i> (%)	Cumulative person-years	Incidence rate (events/person-years × 100)	
Comparison: exclusion of younger patients (second and third decades of life)							
Liver-related death	2/42 (5)	398	0.50	3/12 (25)	92	3.26	6.49 (1.22–34.6)
All-cause death	11/42 (26)		2.76	5/12 (42)		5.43	1.97 (0.84–4.60)
Liver-related adverse outcome	7/42 (17)		1.76	4/12 (33)		4.35	2.47 (0.89–6.87)

Incidence reported as incidence rate (number of measured events/person-years × 100). Person-years correspond to cumulative time of at-risk exposure

AIH autoimmune hepatitis, NASH nonalcoholic steatohepatitis

Summary of clinical data for individuals dying from liver-related or all-cause mortality

Table 5

Case	Age at index biopsy (years)	Sex	Time to death (years)	Cause of death	Liver-related
AIH and NASH cohort					
1	67	F	0	Hepatorenal syndrome secondary to cirrhosis	Yes
2	53	F	8	Acute hepatic failure	Yes
3	56	F	8	Cirrhosis	Yes
4	50	F	5	Sepsis secondary to pneumonia	No
5	78	F	3	Clinical documentation unavailable	No
AIH cohort					
1	51	F	14	Metastatic lung cancer	No
2	47	F	15	Clinical documentation unavailable	No
3	73	M	1	Cirrhosis	Yes
4	63	F	30	Clinical documentation unavailable	No
5	48	M	14	Hepatocellular carcinoma	Yes
6	47	F	9	Clinical documentation unavailable	No
7	56	M	26	Clinical documentation unavailable	No
8	75	F	25	Pneumococcal community acquired pneumonia	No
9	67	F	1	Clinical documentation unavailable	No
10	74	M	0	Clinical documentation unavailable	No
11	74	F	13	Clinical documentation unavailable	No

AIH autoimmune hepatitis, *SS* simple steatosis, *NASH* nonalcoholic steatohepatitis

Table 6

Comparison of long-term histologic outcome by treatment history

	Received Tx after index biopsy (N = 19)	No. Tx after index biopsy (N = 6)	p value Tx versus no Tx
Histologic outcome by treatment history			
Delta grade, mean (SD)	-1.71 (0.90)	0.42 (0.92)	<0.0005
Delta stage, mean (SD)	-0.21 (0.92)	0.58 (0.92)	0.08

The delta grade and delta stage are calculated as the grade or stage on first follow-up biopsy minus the grade or stage on index biopsy, respectively

AIH autoimmune hepatitis, *SS* simple steatosis, *NASH* nonalcoholic steatohepatitis, *No.* number, *Tx* treatment