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Autoimmune Features in Metabolic Liver Disease: A Single-Center Experience and Review of the Literature

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Abstract Non-alcoholic steatohepatitis (NASH) is the progressive phenotype of non-alcoholic fatty liver disease associated with the metabolic syndrome. The existence of autoimmune features in NASH has been reported, but its significance remains unclear. We herein report the autoantibody profile of 54 patients with histologically proven NASH and further determined the development of autoimmunity in three different murine NASH models (monosodium glutamate, CDAA (choline-deficient L-amino acid-defined), and TSOD (Tsumura Suzuki, Obese Diabetes)) at 48 weeks of age. Forty-eight percent (26/54) of NASH cases were positive for antinuclear (ANA) or antimitochondrial antibody and manifested histological signs of overlap with autoimmune hepatitis and primary biliary cirrhosis, respectively. These patients were significantly older (60±10 versus 50±16 years), more frequently women (81 % versus 43 %), and with more severe portal inflammatory infiltrate compared with patients without autoimmunity. In one third of mice, regardless of the model, we observed a marked lymphoid infiltrate with non-suppurative cholangitis, and several cases were ANA-positive, but none AMA-positive. Our data suggest that autoimmunity may share some pathogenetic traits with the chronic inflammation of NASH, possibly related to advanced age.

Keywords Metabolic syndrome · Female sex · Non-alcoholic fatty liver disease

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Abbreviations

AIH	Autoimmune hepatitis
AMA	Anti-mitochondrial antibodies
ANA	Anti-nuclear antibodies
CDAA	Choline-deficient L-amino acid-defined
CNSDC	Chronic non-suppurative destructive cholangitis
IL-6	Interleukin-6
MSG	Monosodium glutamate
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
PBC	Primary biliary cirrhosis
TNF-α	Tumor necrosis factor-α
TSOD	Tsumura Suzuki, Obese Diabetes

Is NASH Autoimmune?

The major cardiovascular risk factors have been recently united in the metabolic syndrome corollarium that represents one of the most serious health issues of the twenty-first century. Non-alcoholic fatty liver disease (NAFLD) is the liver phenotype of the metabolic syndrome [1], and its most severe form, coined non-alcoholic steatohepatitis (NASH), may lead

Table 1 Demographic, clinical, and biochemical characteristics of patients with NASH with (NASH-A) or without (c-NASH) signs of autoimmune disease

	NASH-A	c-NASH	*P* value
Female sex (*n*)	21 (81 %)	12 (43 %)	0.0057
Age (years)	60±10	50±16	0.0090
AST (U/l)	68±43	67±32	NS
ALT (U/l)	84±72	119±113	NS
Obesity (*n*)	23 (89 %)	20 (71 %)	NS
Serum ANA (*n*)	23 (88 %)	0 (0 %)	–
Serum AMA (*n*)	6 (23 %)	0 (0 %)	–

to cirrhosis and hepatocellular carcinoma [2]. Representing the two major autoimmune liver diseases, autoimmune hepatitis (AIH) is characterized by the high-titer anti-nuclear autoantibodies (ANA) and by portal and parenchymal inflammation involving lymphoplasma cells [3] while primary biliary cirrhosis (PBC) manifests interlobular bile duct damage, referred to as chronic non-suppurative destructive cholangitis (CNSDC) that leads to the typical vanishing bile duct syndrome [4]. AIH and PBC are considered to be distinct disease entities with different pathogenetic mechanisms [5]; however, overlap PBC/AIH overlap syndromes are sometimes observed [6]. Anti-mitochondrial autoantibodies (AMA) are reportedly expressed in nearly 100 % of PBC patients [7, 8] while a subgroup of patients will also have serum ANA [9].

We examined the autoimmune features of NASH in a series of patients and in three different models of NASH. First, we investigated the autoantibody and autoimmune pathology prevalence in patients with histologically proven NASH and report that such prevalence is higher in older subjects. Second, we determined the autoimmune features of female NASH mice and observed that these are frequently encountered.

Our Experience with Autoimmunity in NASH

Study Design

Fifty-four patients with a histological diagnosis of NASH [10] were consecutively enrolled at our center and a related hospital in Toyama, Japan (Table 1). Twenty-six patients manifested signs of AIH (n=21) or PBC (n=4) and were diagnosed with one or both (n=1) of these conditions prior to liver biopsy based on internationally accepted criteria [3, 4]; these patients were referred to as NASH with autoimmune features (NASH-A). The remaining 28 cases were referred to as common NASH (c-NASH) and had no signs of autoimmunity. Histological samples from all subjects were blindly reviewed by an experienced liver pathologist (K.T.) who re-scored the degree of portal and parenchymal inflammation in all cases as follows: 0, no inflammation (normal); 1, minimal inflammation; 2, mild inflammation; 3, moderate inflammation; and 4, severe inflammation [11].

We also utilized female mice from three different NASH models, namely monosodium glutamate-induced (MSG, n=6), choline-deficient, L-amino acid-defined (CDAA, n=6), and Tsumura, Suzuki, Obese Diabetes (TSOD, n=10) mice. The first model is induced by neonatal MSG injection and manifest obesity, type 2 diabetes, and NASH when fed a normal diet [12–14]. Second, the CDAA model is established in C57/BL6 mice with a CDAA diet and is characterized by severe NASH [15, 16]. Third, the TSOD mice are an established *ddy* strain from Japan with obesity, type 2 diabetes, NAFLD, and spontaneous hepatocellular carcinoma [17]. All mice were sacrificed after 48 weeks, and liver pathology and serum autoantibodies were blindly evaluated using indirect immunofluorescence and recombinant antigens with ELISA [8].

All data were analyzed using JMP software version 10.0 (SAS Institute, Cary, NC, USA). The Mann–Whitney U test was used to evaluate statistical differences in age distribution and portal and parenchymal inflammation scores between groups. The χ^2 with Fisher's exact test was used to evaluate statistical differences in sex ratios and obesity rates between the two groups. Transaminase levels were analyzed using Student's t test. All analyses were two-tailed, and differences were considered significant with P values of <0.05.

Results

Prior to liver biopsy, 21/26 (81 %) cases of NASH-A had been diagnosed with AIH, 4 (15 %) PBC, and 1 as AIH-PBC

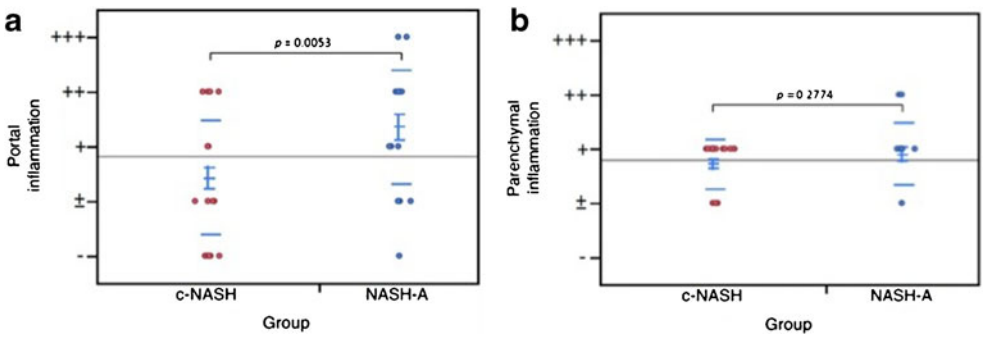

Fig. 1 Histological scoring of inflammation in liver samples from NASH-A and c-NASH cases. **a** Portal inflammation was significantly more severe in the NASH-A group (P=0.0053) while **b** no significant differences were observed in the degree of parenchymal inflammation between groups (P=0.2774)

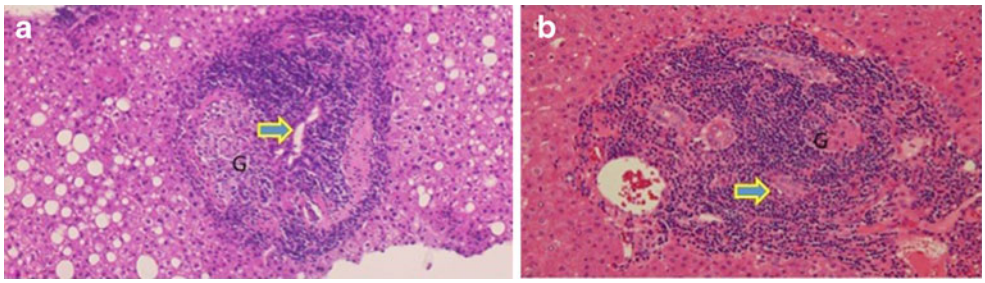

Fig. 2 Liver histology from two representative patients with NASH-A and **a** PBC with marked lymphoplasmatic infiltration with interface hepatitis in the portal tract, epithelioid granuloma (G) in the portal tract, and interlobular bile duct damage mimicking CNSDC (*arrow*) along with macrovesicular steatosis, hepatocellular ballooning degeneration, and mild lobular inflammation with neutrophils or **b** AIH with marked lymphoplasmatic infiltration with interface hepatitis in the portal tract (×200 magnification)

overlap syndrome. Patients with NASH-A were predominantly women (81 %), obese (89 %), and had an average age of 60±10 years. NASH-A and c-NASH did not differ significantly for transaminase levels (AST 68±43 versus 67±32 U/l; ALT 84±72 U/l versus 119±113 U/l; *P*=not significant for both comparisons). Portal but not parenchymal inflammation was more severe in NASH-A than in c-NASH (Fig. 1), and NASH-A frequently had CNSDC-like bile duct injury.

These were virtually indistinguishable from PBC and AIH in addition to lobular inflammation peculiar of NASH in two obese women with serum AMA and ANA, respectively (Fig. 2).

In the proposed NASH murine models, serum ANA were positive in two cases (one MSG, one CDAA) while AMA were not detected. At liver histology, we observed marked lymphoid aggregation with CNSDC-like biliary damage in one third of animals (2/6 MSG, 2/6 CDAA, and 3/10 TSOD mice) (Fig. 3).

What We Know on Autoimmunity and NASH

Autoimmune liver diseases may overlap with any other chronic liver condition, as well represented by hepatitis C infection with serum autoantibodies [18, 19], in some cases induced by antiviral treatments [20]. Nevertheless, the association between chronic infections and tolerance breakdown has been investigated for decades with solid data for putative causality in specific cases [21, 22]. One less obvious connection is the one hypothesized between fatty liver disease and autoimmunity, particularly when alcohol is not involved, and we addressed this issue in the present study. Indeed, we herein report the clinical and biochemical features of a consecutive cohort of patients with histologically proven NASH and identify age and sex as possible cofactors. In a complementary fashion, we report that mice with induced NASH and metabolic syndrome also manifest serum AMA and ANA in a minority of cases. Patients with NASH-A were predominantly women and older compared with c-NASH while portal inflammation was more severe in the former group and in some cases virtually indistinguishable from PBC. In all three animal models included in the study, almost one third of female mice manifested autoimmune features, either serum ANA or portal inflammation with bile duct damage. In our recent past, our group had five different PBC models including both xenobiotic induced and genetically determined ones [23–28] but failed to identify any feature of metabolic syndrome, NAFLD, or NASH (*data not shown*).

The Putative Mechanisms Linking NASH and Autoimmunity

In particular, we may hypothesize that the mechanisms involved in the onset of the metabolic syndrome, NAFLD, and

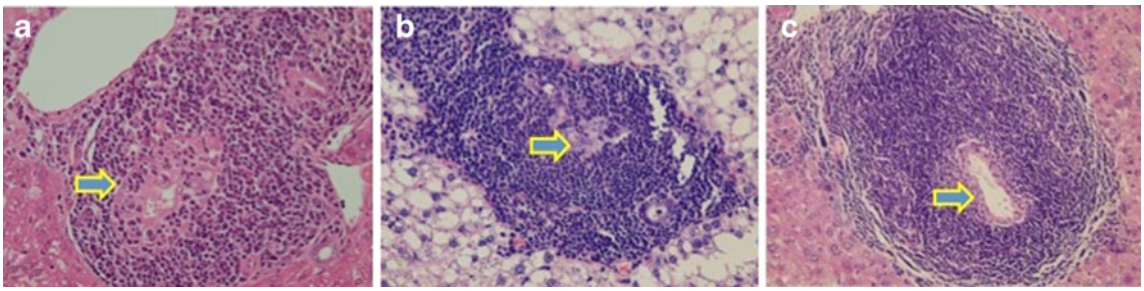

Fig. 3 Liver histology from NASH murine models; MSG (**a**), CDAA (**b**), and TSOD (**c**). In all three models, we observed a marked lymphoplasmatic infiltration with interface hepatitis in the portal tract and interlobular bile duct damage mimicking CNSDC (*arrow*), while metabolic changes were different in the three models (×200 magnification)

NASH may also induce autoimmune features, particularly in older obese women.

Sex The female predominance of autoimmune diseases remains enigmatic despite the numerous observations [29–32] while more data are now available on the effects of nutrition on the immune system [33], possibly mediated by the microbiota changes which also appear to be different in men and women [34–37]. First, sex hormones and age-related events have been considered as factors that may contribute to the development of autoimmune features but data remain inconclusive with the exception of animal models [31, 38]. One complementary evidence to this viewpoint is our recent observation of the protective effects of estrogen and progesterone against drug-induced liver injury, as halothane-induced hepatotoxicity was reduced by estrogen and increased by progesterone pretreatments [39–41]. Second, fetal microchimerism and X monosomy are fascinating candidates for the immune derangement leading to autoimmunity in women [42, 43]. Lastly, hormonal imbalances observed with pregnancy or menopause may modify some of the processes involved in immune-mediated liver damage and vice versa [44].

Cytokines Inflammatory cytokines are modulated by sex and certainly play a role in immune-mediated liver damage. In obese patients, enlarged adipocytes in visceral fat produce inflammatory cytokines such as IL-6 and TNF-α [45] while aggregated macrophages in visceral fat also produce a proinflammatory milieu [46]. Several reports suggest that cholangiocytes under inflammatory conditions express the receptors for TNF- α and IL-6 [47]. Following these lines of evidence, inflammatory cytokines produced by visceral fat may reach the liver through the systemic circulation and react with bile duct epithelial cells expressing cytokine receptors.

Oxidative Stress Another sex- and weight-dependent candidate is oxidative stress which remains a well-known enhancer of both NASH and PBC [48–50]. With ageing, the expression of anti-oxidants such as GST-pi decreases [51], as observed in PBC which is commonly diagnosed after 50 years of age [4, 52]. These observations suggest that aging may per se weaken the processes that protect against oxidative stress and thus facilitate the breakdown of immune tolerance in susceptible elderly women.

Final Remarks

The history of research is rich of examples in which fields that were thought to be fully independent rapidly became connected. Some major examples include innate and adaptive immunity, inflammation and heart disease, or genetics and the environment [44, 53–56]. On a more pragmatic level, we presented here data on the putative connection between metabolic disease and autoimmunity. While we are aware that similar connections were previously proposed for alcoholic disease [57, 58], we are convinced that the link proposed herein is intended to be significantly stronger and to rapidly become crucial. The major strengths of the data presented herein include histology available in all the included NASH cases and the parallel study of three NASH animal models for completeness. Nevertheless, we can only hypothesize that next-generation sequencing [59], microRNA definition [60], and the study of the microbiota could provide new evidence in the coming years while we should not overlook the role of sex [29, 30, 43, 61–63] and ageing [22] in this scenario.

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