ORIGINAL ARTICLE

Centrilobular necrosis in autoimmune hepatitis: a histological feature associated with acute clinical presentation

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Aims: The characteristic histological feature of autoimmune hepatitis (AIH) is interface hepatitis with predominant portal lymphoplasmacytic necroinflammatory infiltration. Centrilobular necrosis (CN), reminiscent of toxic or circulatory liver injury, has been reported in AIH. The aim of this study was to assess the frequency of CN in patients with AIH and its correlation with laboratory and clinical data.

Methods: Liver biopsies were obtained from 114 patients (90 women, 24 men, mean (SD) age 45.4 (19.4) years) with AIH and were evaluated under code by a single pathologist according to the modified Knodell score.

Results: CN was found in 20 (17.5%) patients with virtually unaffected portal areas in four cases. Patients with AIH with CN had a higher total hepatic activity index (median (range) 11 (6 to 15) v 5 (2 to 10)) and presented less frequently with cirrhosis (10% v 38%). Patients with CN had a higher frequency of acute onset (87% v 32%), higher bilirubin (median (range) 12.0 (0.43 to 40.0) v 1.9 (0.36 to 46)) and higher ALT levels (median (range) 25.6 (2.7 to 63.9) v 7.2 (0.7 to 62.6)), than did patients with AIH without centrilobular injury.

Conclusion: CN with sparing of the portal areas represents a rare histological pattern in AIH. CN is associated with an acute clinical presentation and might reflect an early lesion preceding portal involvement. Recognition of this particular histological appearance enables early diagnosis of AIH and a timely initiation of immunosuppressive therapy.

Autoimmune hepatitis (AIH) is characterised by the presence of autoantibodies, hypergammaglobulinaemia, elevated serum transaminases, and the histological evidence of interface hepatitis with a predominantly portal lymphoplasmacytic necroinflammatory infiltrate.¹ In the absence of a “gold standard”, the diagnosis is based on cumulative characteristics of both clinical and histopathological features. With the aim of standardising patients in clinical studies, a revised scoring system, including multiple clinicopathological criteria, has been proposed by the International Autoimmune Hepatitis Study Group (IAIHG).²

Periportal hepatitis with piecemeal necrosis is considered to be the hallmark histological lesion of AIH; however, other histological findings ranging from lobular hepatitis³ to cirrhosis^{4–6} can be found. Centrilobular necrosis (CN) is a nonspecific histological finding caused by hepatotoxins such as acetaminophen,⁷ paracetamol, thioacetamide, tetrachloride,⁸ congestive hepatic injury in veno-occlusive disease and cardiac hepatopathy due to acute right sided cardiac failure,⁹ or hypoxic injury due to ischaemia.⁸ Confluent necrosis of azinar zone 3 may also occur in acute viral hepatitis. In patients undergoing orthotopic liver transplantation CN has been reported in up to 30% of hepatic allografts.¹⁰ It has been linked to acute cellular rejection,^{11–12} ischaemia reperfusion injury,¹³ vascular congestion, and drug toxicity.¹⁴

In about 20–30% of patients, AIH presents with acute clinical features similar to manifestations of other acute liver diseases with possible progression to acute liver failure,¹⁵ but the histological appearance of acute autoimmune hepatitis is poorly defined.^{16–17} Cases of patients with AIH with a recent onset of disease and a predominance of centrilobular injury without significant changes in the portal and periportal areas have been reported.^{18–20} Follow up biopsies performed in some

of these patients revealed a histological pattern more consistent with AIH.^{19–21} This is an important observation, as failure to recognise the histological appearance at the time of acute presentation may lead to a delay in initiation of an appropriate therapy with far reaching consequences as progression to liver cirrhosis and liver failure, particularly as patients might initially present with normal immunoglobulins and even without autoantibodies.²¹

The aim of the present study was to evaluate the frequency of CN and to investigate the correlation of histological appearance with clinical and laboratory data in a large cohort of patients with AIH.

PATIENTS AND METHODS

Patients

In total, 114 consecutive records of patients with AIH (24 men, 90 women; mean (SD) age 45.4 (19.4)) seen in our department were reviewed according to the revised scoring system of the IAIHG.² No patient had evidence of other liver diseases such as viral hepatitis or features of haemochromatosis, Wilson disease, or primary biliary cirrhosis. Patients with overlap syndromes and patients with alcohol intake of >50 g (men) or >25 g (women) daily were excluded from the study. Treatment with steroids was initiated as soon as the diagnosis of AIH was made. Treatment responses were classified according to the criteria of the IAIHG.²

Abbreviations: AIH, autoimmune hepatitis; AMA, antimitochondrial antibodies; ANA, anti-nuclear antibodies; CN, centrilobular necrosis; HAI, hepatic activity index; IAIHG, International Autoimmune Hepatitis Study Group; LKM, liver kidney microsomes; OLT, orthotopic liver transplantation; SMA, smooth muscle antibodies

Detection of autoantibodies

The determination of autoantibodies was performed in one single laboratory by indirect immunofluorescence to components of the nuclei (anti-nuclear antibodies; ANA), smooth muscle (smooth muscle antibodies; SMA) and mitochondria (antimitochondrial antibodies; AMA) using commercially available Hep-2 cell substrates (MBL, Nagaya, Japan) and rodent tissue (kidney, stomach) preparations (Kallestad; Biorad, Houston, TX, USA). Sera were considered positive at a dilution of 1:40. Liver kidney microsomes (LKM) type 1 autoantibodies (anti-LKM) were detected by indirect immunofluorescence of rodent liver and kidney cryostat sections (Biorad). LKM positive sera were also tested using Ouchterlony double diffusion for reactivity against microsomal antigens using rat liver soluble fractions.

Histological evaluation

Before treatment was initiated, liver biopsies were obtained by the Menghini technique using a 1.4 or 1.6 G needle (Hepafix; Braun, Germany). Sections were stained with haematoxylin and eosin, and chromotrop anilinblue trichrome and for cytokeratin 7 by immunohistochemistry (anti-CK7; Dako, Vienna, Austria). A single pathologist (FW), blinded to the clinical data, assessed histopathological changes by grading/staging portal inflammation (1–4), portal and periportal hepatitis (0–4), hepatocyte rosette formation (0–3), apoptotic/lytic necrosis (0–4), confluent or bridging necrosis (0–6), and fibrosis (0–6) according to the Ishak grading and staging system.²² Bile duct changes (proliferation) were evaluated on haematoxylin and eosin stained sections and by immunohistochemistry staining for cytokeratin 7 (0–3).

Data presentation and statistical analysis

Comparisons between means were performed by Student's *t* test. The Mann-Whitney *U* test was used for non-normally distributed data as tested by the Kolmogorov-Smirnov test. Differences of distribution between groups were assessed by use of the χ^2 test. A commercially available computer program (SPSS 10.0; SPSS Inc., Chicago, IL, USA) was used for all statistical calculations, and $p < 0.05$ (two tailed) was considered statistically significant.

RESULTS

Of the 114 patients, 95 (83.3%) met the criteria for a definite diagnosis, and 19 (16.7%) were scored as having probable AIH according to the revised criteria of the IAIHG.² The mean (SD) AIH score was 20.5 (3.6). In total, 100 (87.7%) were positive for ANA and/or ASMA, 2 patients (1.7%) tested positive for LKM antibodies, and 19 patients (16.7%) positive for SLA. The mean (SD) number of portal tracts per liver biopsy specimen was 10.9 (6.7). Total HAI was 5 (2 to 15) (median (range)). Interface hepatitis was found in 100 (87.7%), and liver cell rosettes in 85 patients (74.5%). In 20 patients (17.5%), centrilobular necrosis was present in the liver biopsy. In four of the 20 cases with CN (= 3.5% of all patients) the portal tracts were virtually unaffected. Fig 1 shows the haematoxylin and eosin stained section of a liver biopsy of one of these patients. Overall, 38 patients (33.3%) had histological signs of liver cirrhosis at the time of diagnosis (2 of 20 patients with CN compared with 36 of 94 patients without CN; $p = 0.015$, table 1). The stage of fibrosis was lower in patients with centrilobular injury (median (range) 3 (1 to 6) *v* 5 (1 to 6), $p = 0.024$, table 1). Portal and lobular changes and total hepatic activity index (11 (6 to 15) *v* 5 (2 to 10), $p < 0.001$, table 1) were higher in patients with CN compared with patients without.

Acute onset of disease was more common in patients with CN (87% *v* 32%, $p < 0.001$). Transaminases were higher in

Figure 1 Liver biopsy specimen. Central vein is indicated by arrow, portal tract by arrowhead. (A, B) Centrilobular area with surrounding necrotic hepatocyte loss and absence of parenchymal inflammation. (C) Portal tract with minimal inflammatory infiltrate and minimal interface hepatitis.

patients with zone 3 necrosis compared with patients without ($\times$ ULN median (range): ALT 25.6 (2.7 to 63.9) *v* 7.2 (0.7 to 62.6), $p < 0.001$; AST 24.5 (2.2 to 53.7) *v* 6.0 (1.1 to 86.5); $p < 0.001$, table 1). Furthermore, bilirubin levels were higher in patients with centrilobular injury (median (range) 12.0 (0.43 to 40.0) *v* 1.9 (0.36 to 46) mg/dl; $p < 0.001$, table 1). Patients with or without CN did not differ in terms of age, total IAIHG score, or percentage of reaching a definite/probable diagnosis (table 1) according to the IAIHG score. Total immunoglobulins tended to be lower in patients with CN ($p = 0.14$; table 1). Clinical and serological data of patients with CN are shown in table 2. Two patients (nos. 12 and 15, table 2) had undetectable autoantibodies and normal immunoglobulins at initial presentation. In one patient (no. 15) ANA (1:80) became detectable at second determination, while the other patient remained seronegative.

Table 1 Clinical and laboratory data of patients with AIH and centrilobular necrosis (CN) versus patients without centrilobular necrosis

	With CN	Without CN	p
No. of patients (M/F)	20 (3/17)	94 (21/73)	
Mean (SD) age (years)	47.1 (14.7)	45.0 (20.3)	0.78
Acute onset (n/%)	17/87%	30/32%	0.001
IAIHG score*	20 (3.1)	21 (2.8)	0.86
Definite AIH (N/%)	15/75%	80/85.1%	0.538
Probable AIH (N/%)	5/25%	14/14.9%	
Bilirubin (mg/dl)	12.0 (0.43 to 40.0)	1.9 (0.36 to 46)	0.001
ALT (×ULN)	25.6 (2.7 to 63.9)	7.2 (0.7 to 62.6)	0.001
AST (×ULN)	24.5 (2.2 to 53.7)	6.0 (1.1 to 86.5)	0.001
IgG (×ULN)	1.28 (0.3 to 3.15)	1.43 (0.48 to 4.8)	0.14
Portal changes			
Portal inflammation (1–4) (mean (SD))	2.4 (0.8)	1.7 (0.6)	0.001
Interface hepatitis (0–4)	3 (1 to 4)	2 (1 to 4)	0.001
Lobular changes			
Spotty necrosis (0–4)	2 (0 to 4)	1 (0 to 3)	0.001
Confluent necrosis (0–6)	3.5 (2 to 6)	0 (0 to 1)	0.001
Total HAI	11 (6 to 15)	5 (2 to 10)	0.001
Fibrosis	3 (1 to 6)	5 (1 to 6)	0.024
Cirrhosis (n/%)	2/10	30/38	0.015

*An aggregate score >17 following therapy constitutes a definite diagnosis of AIH, a score of 12–17 after therapy is considered probable for the diagnosis of AIH. Data are median (range) unless otherwise indicated. ULN, upper limit of normal. Bold type indicates significance.

DISCUSSION

In the absence of typical clinical or laboratory features, diagnosis of AIH is a major challenge. This study investigated the role of liver histology for diagnosis of AIH with a specific focus on the presence of CN. The predominant histopathological pattern of AIH is interface hepatitis with portal and periportal plasma cells with or without lobular hepatitis. However, these histological findings have a poor specificity (81%), sensitivity (40%), and positive predictive value (68%).^{6–23} Furthermore, they only represent part of a broad spectrum of morphological changes including hepatocyte rosettes, incidental bile duct injury,²⁴ and different stages of fibrosis.^{4–6}

CN was observed in 17.5% of our patients with AIH, with sparing of the portal tracts in 3.5% of cases. Patients with CN more frequently had an acute onset of disease and a lower frequency of cirrhosis than those without. Similarly, in a recent study of six patients with AIH and CN, none presented

with liver cirrhosis.²¹ Remarkably, only one of these patients had elevated immunoglobulines and one patient was initially negative for autoantibodies.²¹ In contrast, in other studies focusing on patients with acute onset AIH, lobular hepatitis (but not CN) was identified as a prominent histological finding.³ One possible explanation for this unusual presentation of AIH is that CN reflects an early lesion in AIH. In a murine model of AIH, the initial histological inflammatory infiltrates preferentially occurred around the central vein.²⁵ Furthermore, follow up biopsies from patients with CN demonstrated the evolution of periportal infiltrates more typically associated with AIH.^{18–19} However, persistence of CN during sequential biopsies has been reported.²¹ If CN reflects an early lesion in AIH, one would expect to find it more frequently. The occurrence of CN in AIH may be underestimated because CN (especially with sparing of the portal tracts) is not considered pathognomonic for AIH. On the other hand, acute onset AIH may simply be a sign of an acute

Table 2 Clinical and serological features of patients with CN

Patient no.	Age/sex	ANA	SMA	SLA	IgG (×ULN)	HLA DR3/DR4	IAIHG score*
1	69/F	1:40	Neg	Neg	0.9	HLA-DR 3	19
2	58/F	Neg	1:640	Neg	3.2	–	22
3	50/F	1:80	Neg	Pos	2.0	–	23
4	58/F	1:160	1:1280	Neg	2.2	HLA-DR3	26
5	42/M	1:40	1:320	Neg	1.1	HLA-DR3	17
6	54/F	Neg	1:80	Neg	1.3	–	19
7	17/F	Neg	Neg	Pos	0.6	–	19
8	57/F	Neg	1:640	Neg	2.5	–	23
9	35/F	1:1280	1:40	Neg	1.3	–	21
10	39/M	Neg	1:160	Neg	1.47	HLA-DR3	16
11	46/F	1:640	Neg	Neg	0.9	HLA-DR3	20
12	32/M	Neg	Neg	Neg	0.30	–	14
13	62/F	1:1280	Neg	Neg	1.53	HLA-DR4	25
14	20/F	1:40	Neg	Neg	0.66	HLA-DR4	17
15	25/F	Neg	Neg	Neg	0.90	–	17
16	49/F	1:320	Neg	Neg	1.42	HLA-DR3	20
17	58/F	1:640	Neg	Neg	0.69	HLA-DR3	21
18	59/F	1:640	1:40	Neg	1.64	–	22
19	59/F	Neg	Neg	Pos	1.17	–	19
20	52/F	1:80	1:640	Neg	1.31	HLA-DR3	24

Autoantibodies were considered positive at a titre ≥1:40. No patient had a history of alcohol abuse, recent drug exposure, detectable AMA, an ALP/ALT ratio of >1.5 or markers of hepatitis B or C virus infection. No patient had detectable LKM. ULN, upper limit of normal. *Post-treatment.

TAKE HOME MESSAGES

- Centrilobular necrosis (CN), reminiscent of toxic or circulatory liver injury, has been reported in autoimmune hepatitis (AIH).
- CN was observed in 17.5% of patients with AIH, with sparing of the portal tracts in 3.5% of cases.
- Patients with CN more frequently had an acute onset of disease and a lower frequency of cirrhosis than those without.
- CN is associated with an acute clinical presentation and might reflect an early lesion preceding portal involvement.

exacerbation of pre-existing chronic AIH.^{3 16 17} In this study, only 10% of the patients with CN (in contrast to 38% of those without) presented with liver cirrhosis at time of diagnosis, thus CN is more common in patients with less advanced disease. Finally, CN is a non-specific histological feature, so one might suggest that especially those patients with few portal and periportal changes may have liver diseases other than AIH. CN is usually associated with vascular (ischaemic or congestive) or drug induced hepatic injury, as this localisation reflects the area where substances are preferentially metabolised to their hepatotoxic metabolites, or uptake by zonally distributed receptors is maintained. None of our patients with CN was taking medications or herbal remedies causing drug induced hepatitis. There was also no evidence of hepatic veno-occlusive disease, cardiac hepatopathy, hepatic ischaemia, or acute hepatitis due to known viruses. In addition, these patients responded well to immunosuppressive therapy. Based on the revised IAIHG scoring system, diagnosis of "definite AIH" (aggregate score >17) was not possible in five patients with CN (tables 1, 2). Two patients tested negative for autoantibodies at initial determination. One of them developed autoantibodies during follow up, while the other remained seronegative. Appearance of autoantibodies has also been observed also by others during follow up of patients with AIH and CN, adding additional evidence that CN might be an early lesion in AIH.^{18 19 21}

CN is also found in "allogenic" immune response in liver transplant recipients. De novo and recurrent AIH with CN has been reported after orthotopic liver transplantation.^{26–28} Acute rejection can present as isolated zone 3 inflammation without portal inflammation or bile duct injury.^{12 14} Immunosuppressive therapy of acute rejection with CN appears to reverse the process in the majority of cases and may thus prevent the evolution towards chronic rejection and graft loss.^{28–30} CN has also been associated with an increased incidence of chronic rejection.^{10 12 28 31}

In summary, CN (with sparing of the portal tracts) represents an infrequent histopathological feature of autoimmune hepatitis and may reflect an early stage of the disease associated with an acute clinical presentation. However, CN also occurs, although less frequently, in advanced stages of AIH. Thus, lobular flare of disease activity appears to be more common in patients with less advanced disease than in those with advanced disease. Early recognition of AIH by this distinctive histological pattern allows a timely initiation of immunosuppressive therapy.

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