Jikeikai Med J 2023 ; 70 : 1-10

Morphogenetic Process of Portal Tract Involvement and Portal Vein Damage in the Noncirrhotic Stage of Adult Nonalcoholic Steatohepatitis : A 3-dimensional Approach

Hiroshi HANO[1,2]

[1]*Tokyo Jikei-kai Association (Tokyo Jikei-kai)*
[2]*Department of Pathology, The Jikei University School of Medicine*

ABSTRACT

Background : Although adult nonalcoholic steatohepatitis (NASH) leads to liver cirrhosis, the portal tracts are often almost completely preserved in contrast to the relatively progressive fibrosis around the hepatic veins in the early noncirrhotic stage of the disease. Therefore, the early and consecutive process of involvement of the portal tracts and portal veins in this stage was morphologically examined.

Materials and methods : Liver specimens obtained from 2 adult patients with the noncirrhotic stage of NASH were examined. A tissue reconstruction method was used for 3-dimensional observation of histological serial sections. The portal tracts with narrow and broad fibrous bridging to the fibrotic region around the hepatic veins were examined.

Results : Although the 2 patients differed in disease progression, the portal tracts in both patients generally showed only minimal to mild fibrosis and inflammation. These findings indicated early portal tracts involvement due to the spread of the lesions around the hepatic veins. Three-dimensional observations also revealed that as inflammation and fibrosis of the portal tract became severe, portal vein damage became gradually apparent.

Conclusions : The spread of inflammation and fibrosis around the hepatic veins is considered to trigger portal tract involvement in NASH, followed by bridging fibrosis and damage to portal veins.

(Jikeikai Med J 2023 ; 70 : 1-10)

Key words : nonalcoholic steatohepatitis, inflammation, fibrosis, portal tract involvement, portal vein damage

INTRODUCTION

The histologic changes to the liver in nonalcoholic steatohepatitis (NASH) are similar to those in alcoholic liver disease[1]. According to staging for fibrosis severity of the histological scoring systems proposed by Brunt et al.[2], Kleiner et al.[3] and Bedossa et al.[4], NASH begins with centrilobular fibrosis and then progresses to portal fibrosis and bridging fibrosis (BF). Finally, NASH can advance to liver cirrhosis[5-9].

Liver cirrhosis is known to morphologically result from lobular restructuring that develops after the normal angioarchitecture becomes distorted when portal veins are severely damaged owing to chronic liver disease[10-12]. Inflammation, fibrosis, and portal vein damage obviously affect the long-term process of lobular restructuring. Therefore, if

Received : January 28, 2022 / Accepted : February 24, 2023
羽野　寛
Mailing address : Hiroshi HANO, Tokyo Jikei-kai association, 3-25-8 Nishi-shimbashi, Minato-ku, Tokyo 105-8461, Japan.
E-mail : hhano@jikei.ac.jp

these histological factors are precisely assessed, the state of disease progression in NASH and other chronic liver diseases can be better understood.

In the early noncirrhotic stage of NASH with no lobular distortion, despite significant inflammation and fibrosis in the centrilobular region, the portal tracts are preserved or show only mild inflammation and periportal fibrosis. Lobular distortion refers to the lobular architecture being distorted owing to the altered angioarchitecture. The angioarchitectural framework of the liver lobule consists of the portal vein of the parenchymal portion. In the altered angioarchitecture, the arrangement of portal tracts in the periphery of the classical hexagonal lobule and central veins is distorted such as with portal-portal or portal-central fibrous bridging.

However, early and continuous involvement of the portal tracts has not been interpreted in detail. The same is true for portal vein damage. Therefore, the main purpose of the present study was to clarify portal tract and vein involvement in detail in the noncirrhotic stage of NASH. A histological reconstruction method was used for 3-dimensional observation from the point of view of the formal pathogenesis of NASH. Pediatric NASH was not included in this study.

MATERIALS AND METHODS

This retrospective study was approved by the ethics committee of The Jikei University School of Medicine (No. 6126), which waived the requirement of informed consent. I confirm that all methods in this study were performed in accordance with the relevant guidelines and regulations.

Two specimens from 2 patients—1 who had died and had undergone an autopsy and 1 who had undergone surgical resection—were used in this study because they differed in the disease progression in the noncirrhotic stage of NASH and were the most suitable for histological serial sections to be prepared. The autopsy specimens were the same as from the fourth case in a study by Hano et al.[13]. In the present study new data were created for the current purpose of clarifying portal tract and vein involvement in the noncirrhotic stage of NASH. For the patient who had undergone surgery, partial hepatectomy had been performed to remove a hepatic tumor. The tissue blocks were fixed in 10% formalin and embedded in paraffin wax. For histological evaluation the sections were stained with hematoxylin and eosin, Masson's trichrome, periodic acid-Schiff, and silver impregnation. Additionally, serial sections were cut (4 μm) and stained with Masson's trichrome for 3-dimensional observation with a tissue reconstruction method[14]. Microscopic images captured with a Nikon Digital Sight DS-Fi2 camera and the NIS-Elements, version 4.00, software program (Nikon Corporation, Tokyo, Japan) were printed, and outlines of the essential architectural elements were drawn freehand serially on sheets of tracing paper.

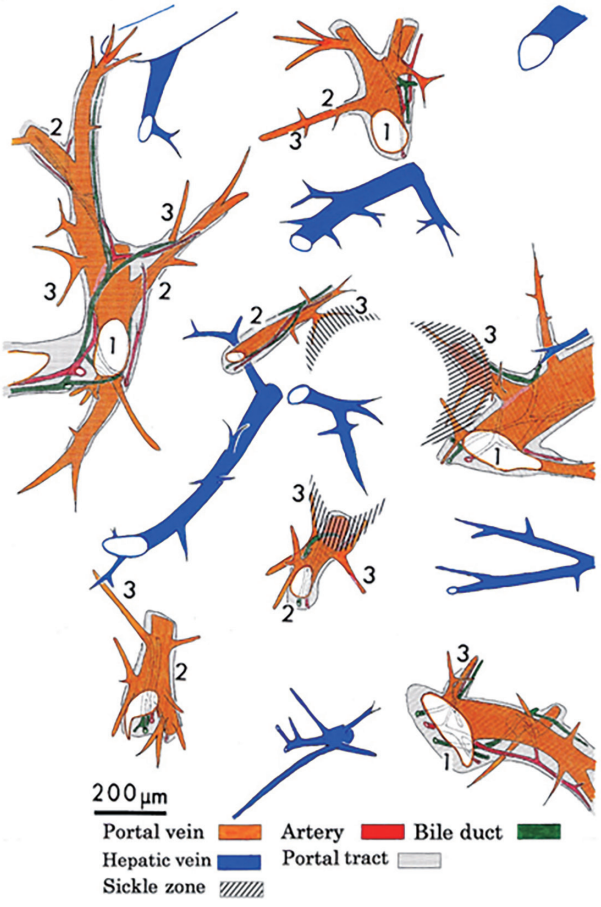

Fig. 1. Histological reconstruction of the normal liver at moderate magnification. The figure covers the parenchymal portion of the portal system composed of 3 step branches. Note the alternating arrangement of portal and hepatic veins and the regular manner of ramification in the portal system. The third step branches form a basic structure of the liver lobule. Adjoining third step branches form a sickle zone with high potential blood flow (hatched line area). 1 : first-step branch, 2 : second-step branch, 3 : third-step branch. Figure reproduced from Hano et al. (16) with permission of Springer Nature.

The reconstruction was completed by step-by-step overlapping of these outlines.

The arteries and bile ducts were simplified or omitted from the outline to focus on the angioarchitecture of the portal vein and venous drainage systems.

Findings of the angioarchitecture in histological graphic reconstructions were compared with those of the normal liver which had been reported in detail by Matsumoto et al.[14,15]. The terms and concepts defined by Matsumoto et al. were used. Matsumoto et al. divided the portal system into a conducting portion and a parenchymal portion. Both portions function to transport the blood, but the parenchymal portion also provides an angioarchitectural framework for the liver lobule. The portal veins of the parenchymal portion comprise the first, second, and third step branches (1st-Br, 2nd-Br, and 3rd-Br). The angioarchitecture of the normal liver (Fig. 1) is quoted from the study by Hano et al.[16].

Results

The clinical data, grade of inflammatory activity, and stage of fibrosis of the 2 patients according to the NASH Clinical Research Network system (3) are shown in Tables 1 and 2.

None of the patients had a history of alcohol abuse or serological findings indicating hepatitis B or C.

Patient 1 was of a 37-year-old Japanese man had been

Table 1. Clinical data of the 2 patients

Clinical data	Patient 1	Patient 2
Main clinical diagnosis	Infarction of the medulla oblongata	Hepatocellular carcinoma
Body mass index (kg/m^2)	32.9	34.6
Aspartate aminotransferase (IU/l)	35	32
Alanine aminotransferase (IU/l)	61	37
γ Guanosine triphosphate (IU/l)	152	54
Triglyceride (mg/dl)	233	127
Total cholesterol (mg/dl)	102	273

Table 2. Histological features 2 patients according to the NASH Clinical Research Network system

Histological features	Patient 1	Patient 2
Steatosis		
Grade	34%-64%	5%-33%
Location	zone 3	zone 3
Microvesicular steatosis	not present	not present
Fibrosis		
Stage	3 (bridging fibrosis)	3 (bridging fibrosis)
Inflammation		
Lobular inflammation	< 2 foci	< 2 foci
Microgranulomas	absent	absent
Large lipogranulomas	absent	absent
Portal inflammation	none to minimal	greater than minimal
Liver cell injury		
Ballooning	many cells/prominent	many cells/prominent
Acidophilic bodies	none to rare	none to rare
Pigmented macrophages	none to rare	none to rare
Megamitochondria	none to rare	none to rare
Other findings		
Mallory hyaline	none to rare	none to rare
Glycogenated nuclei	none to rare	none to rare
Nonalcoholic fatty liver disease activity score	5	4

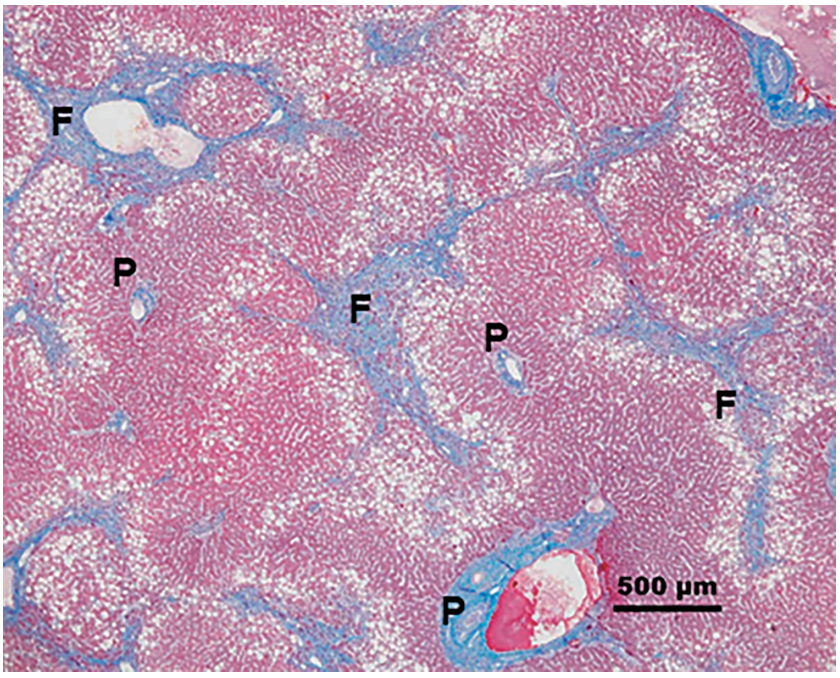

Fig. 2. Photomicrograph showing the general histologic features of patient 1. Fibrosis (F) progresses around the sublobular and central veins, and fibrous tissues become connected (i.e., bridging fibrosis). The portal tracts (P) are almost completely preserved (Masson's trichrome).

treated with a medication for schizophrenia. He had also received diagnoses of prediabetes, hyperlipidemia, and hypertension. He died suddenly 1 week after the onset of medulla oblongata infarction. An autopsy was performed 1.5 hours after his death.

General histological features of patient 1 shown at low magnification (Fig. 2) included markedly progressive fibrosis around the sublobular and the central veins (SCVs). Frequently observed was BF between the fibrotic areas around the SCV (BF-SCV). The fibrotic lesions were associated with mild to moderate inflammation. The distal portal tracts exhibited mild inflammation and fibrosis in places. Occasionally developed was BF between the portal tract and SCV (BF-PSCV).

Two lesions with BF-PSCV were selected for examination with the histological reconstruction method because the portal tracts themselves were almost completely undamaged in appearance except for narrow BF.

Histological features corresponding to the first reconstructed lesion (Fig. 3A) included fibrosis that had expanded widely and irregularly around the hepatic veins with mild lymphocytic infiltration. Although the histological appearance of the portal tract was almost completely preserved except for BF, mild lymphocytic infiltration and minimal periportal fibrosis were present. Moderate macrovesicular steatosis with a zonal distribution pattern developed and ballooning cells were observed to be scattered in the parenchyma.

The first reconstruction was 144 μm thick (a total of 36 sections) and comprised an entire thickness of BF (Fig. 3B). Fibrotic lesions occurred around the SCV and spread to fuse into a broad fibrotic area with arterial development. The spatial arrangement of the distal branches of the hepatic vein was distorted. In contrast, the portal tract exhibited only slight periportal fibrosis. The portal veins and arteries were almost completely preserved. A narrow fibrous bridge developed in BF-PSCV. Only a few small thin-walled vessels, with neither a portal vein nor artery, were observed.

Histological features corresponding to the second reconstructed lesion (Fig. 3C) included fibrosis having developed concentrically around the hepatic vein. Mild lymphocytic infiltration was also present in the fibrotic region. The portal tract was connected to the fibrotic region having narrow BF. The portal tract itself was mildly inflamed with lymphocytic infiltration but was not fibrously enlarged. A small artery was observed in the upper fibrous bridge.

The second histological reconstruction was 84 μm thick (a total of 24 sections) and comprised an entire thick-

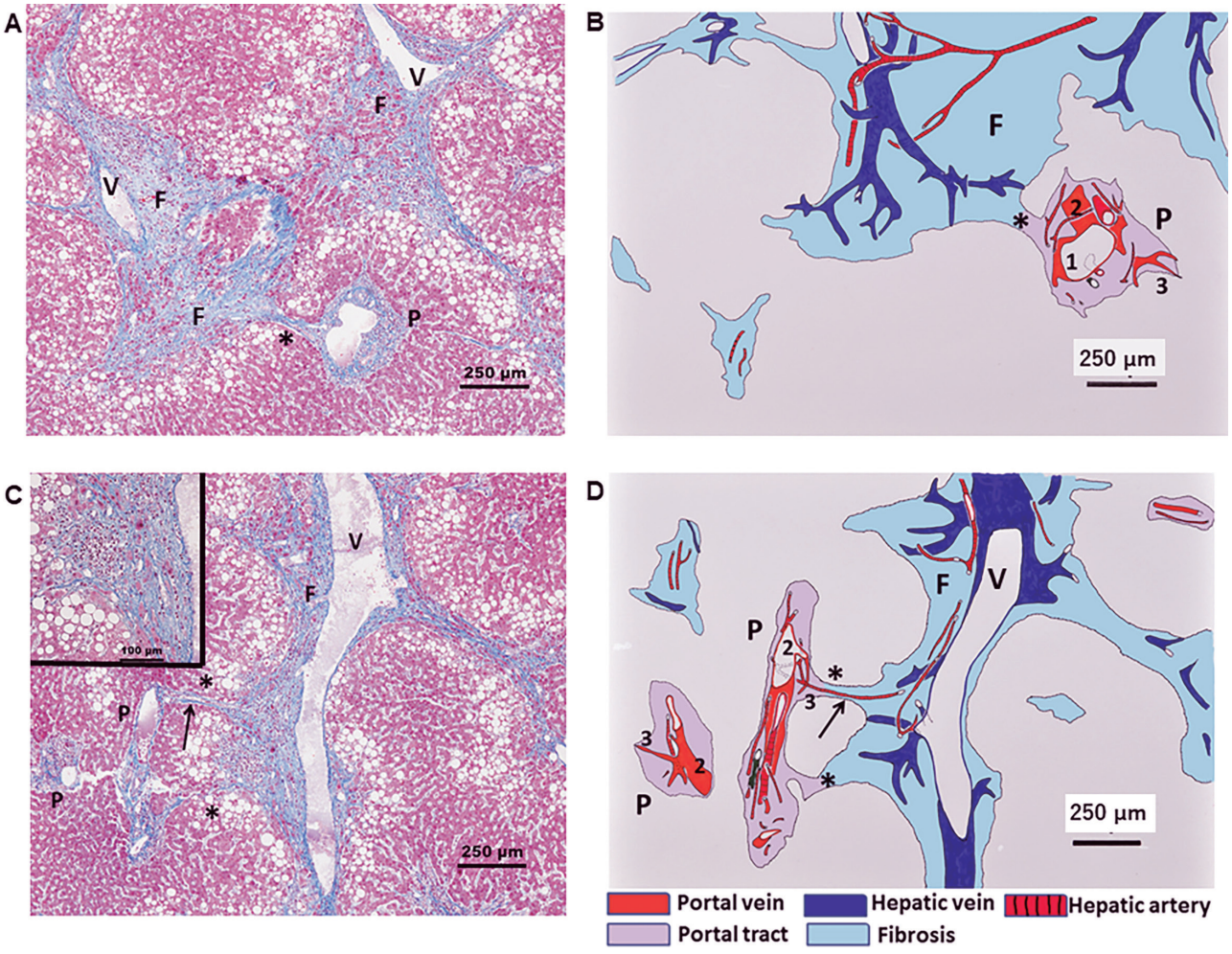

Fig. 3. Histology and histologic reconstruction of patient 1. A : Photomicrograph showing the histology of the first reconstructed lesion shown in B. Bridging fibrosis (asterisk) is observed between the widely expanding fibrotic region (F) around the hepatic veins (V) and portal tract (P). Note that the portal tract is almost completely preserved. Moderate macrovesicular steatosis with a zonal distribution pattern appears around the fibrotic region (F) (Masson's trichrome). B : Histologic reconstruction of the first lesion. Fibrosis (F) widely spreading around the sublobular and central veins with aberrant arterial development is present. The distal branches of the hepatic veins become thicker and ramify irregularly. In contrast, the portal tract (P) shows only slight fibrous enlargement, and the angioarchitecture is largely maintained. Bridging fibrosis (asterisk) is present. 1 : first-step branch ; 2 : second-step branch ; 3 : third-step branch. C : Photomicrograph showing the histology of the second reconstructed lesion shown in D. Bridging fibrosis (asterisks) is observed between the fibrotic region (F) concentrically developing around the hepatic veins (V) and portal tract (P). A small artery runs in the upper fibrous bridging (arrow). Inset : Photomicrograph at higher magnification. Note lymphocytic infiltration in the fibrotic region and parenchyma (Masson's trichrome). D : Histologic reconstruction of the second lesion. Two regions of bridging fibrosis (asterisks) have developed between the fibrotic region around the sublobular vein (V) with its preexisting small branches and portal tract (P). The angioarchitecture in the portal tract is largely preserved. The artery runs from the portal tract toward the sublobular vein through fibrous bridging (arrow). Arterial development is also seen around the sublobular vein (V). The sublobular vein gives off its branches almost regularly.

ness of the BF (Fig. 3D). Fibrosis arose and evolved around the SCV with arterial development. The structure of portal tract was almost completely preserved, and the 2nd-Brs and 3rd-Brs were not damaged. There were 2 narrow BF-PSCVs. A small artery ran from the portal tract to the fibrotic region in the upper fibrous bridge. The newly developed artery had clearly originated from the preexisting artery in the portal tract.

The second patient was a 74-year-old Japanese man who had severe obesity with a body mass index of 34.6 kg/m^2. The patient had been medicinally treated for hypertension and hypothyroidism. While being followed up and ob-

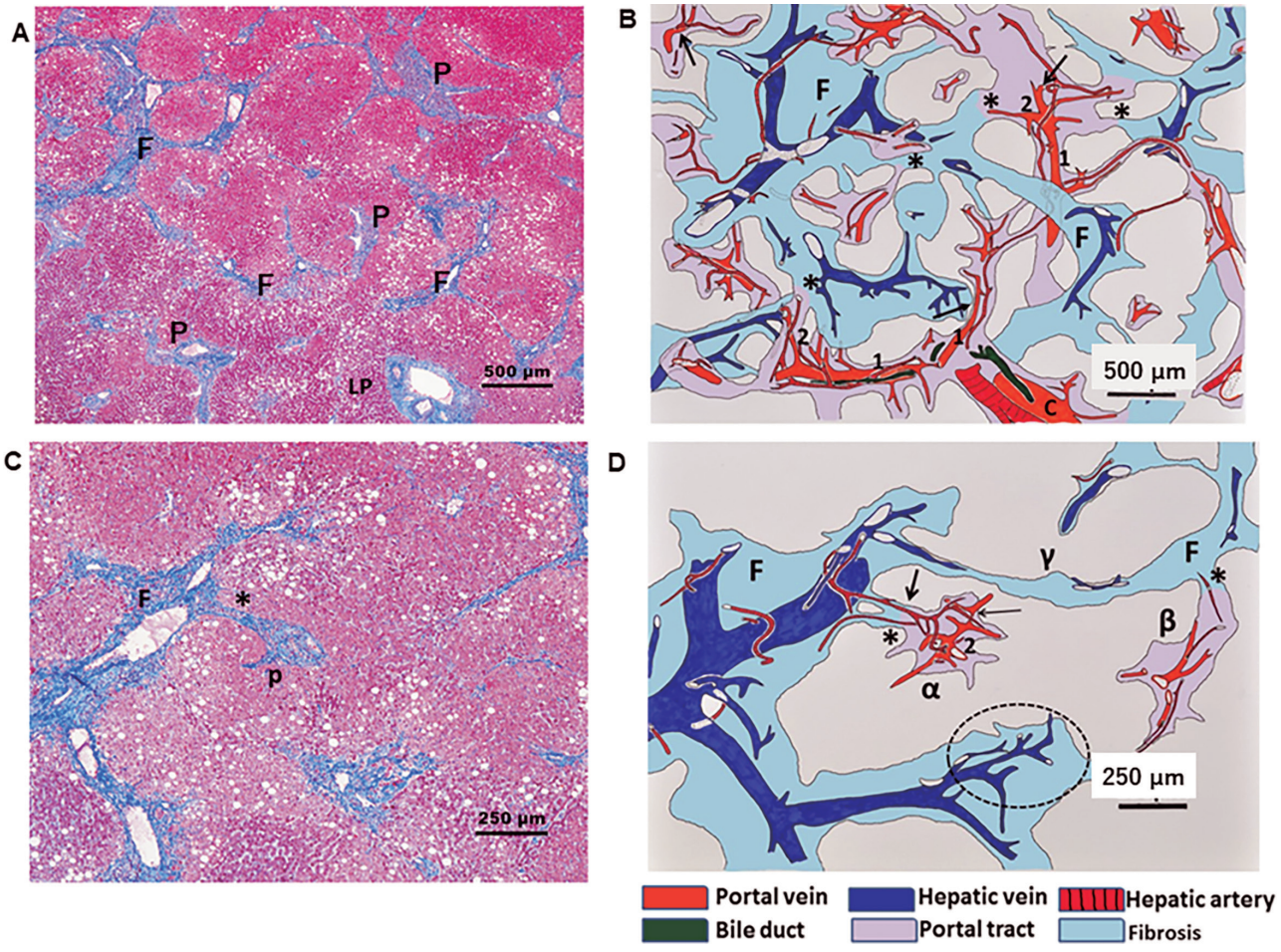

Fig. 4. Histology and histologic graphic reconstruction of patient 2. A : Photomicrograph of the reconstructed area shown in B. Distal portal tracts (P) are predominantly present. Septum-like fibrosis (F) involving hepatic veins is extensively developed. The portal tracts are slightly enlarged with fibrosis. Mild to moderate macrovesicular steatosis is seen. (Masson's trichrome). LP : large portal tract of the conducting portion. B : Histologic reconstruction at low magnification. The portal tracts show mild to moderate fibrous enlargement in places. Expanding fibrosis (F) around the sublobular and central veins is frequently fused into an irregular fibrous network. Bridging fibrosis is frequently present (asterisks). The first step branches (1), second step branches (2), and accompanying arteries are generally maintained, although distortion of the branching and the course of the portal vein is observed in a few places such as a decrease of branches, an abrupt bend and mildly curved running (arrows). C : conducting portion. C : Photomicrograph of the reconstructed area shown in D. The bridging fibrosis is present between the fibrotic region (F) around the hepatic veins and portal tract (P). These regions are mildly inflamed. Additionally, the portal tract is mildly enlarged with portal vein stenosis (Masson's trichrome). D : Histologic reconstruction of the first lesion. Two regions of bridging fibrosis are present (asterisks) between the portal tracts (α , β) and the fibrotic regions (F) around the sublobular and central veins. In portal tract α , the small branches equivalent to the third step branches run irregularly and exhibit an intricate branching pattern with stenosis (thin arrow) and arteries running to the fibrotic region (F) through the bridging fibrosis from the portal tract (thick arrow). The portal veins in portal tract β show less damage than those in portal tract α . The bridging fibrosis between the hepatic veins is indicated by γ . The distal branches of the hepatic vein irregularly ramify, curve and, run in close proximity (dotted-lined circle).

served for diabetes mellitus, a check-up incidentally detected a hepatic tumor, which was resected via a partial hepatectomy. Pathological examination revealed that the tumor was a NASH-related well-differentiated hepatocellular carcinoma. The specimens of liver tissue used in the present study had been surgically resected. Inflammation and portal tract damage were generally more severe in patient 2 (Fig. 4A) than in patient 1 (Fig. 2).

Histological reconstruction was performed at low and high magnifications. In the region of the reconstruction at a

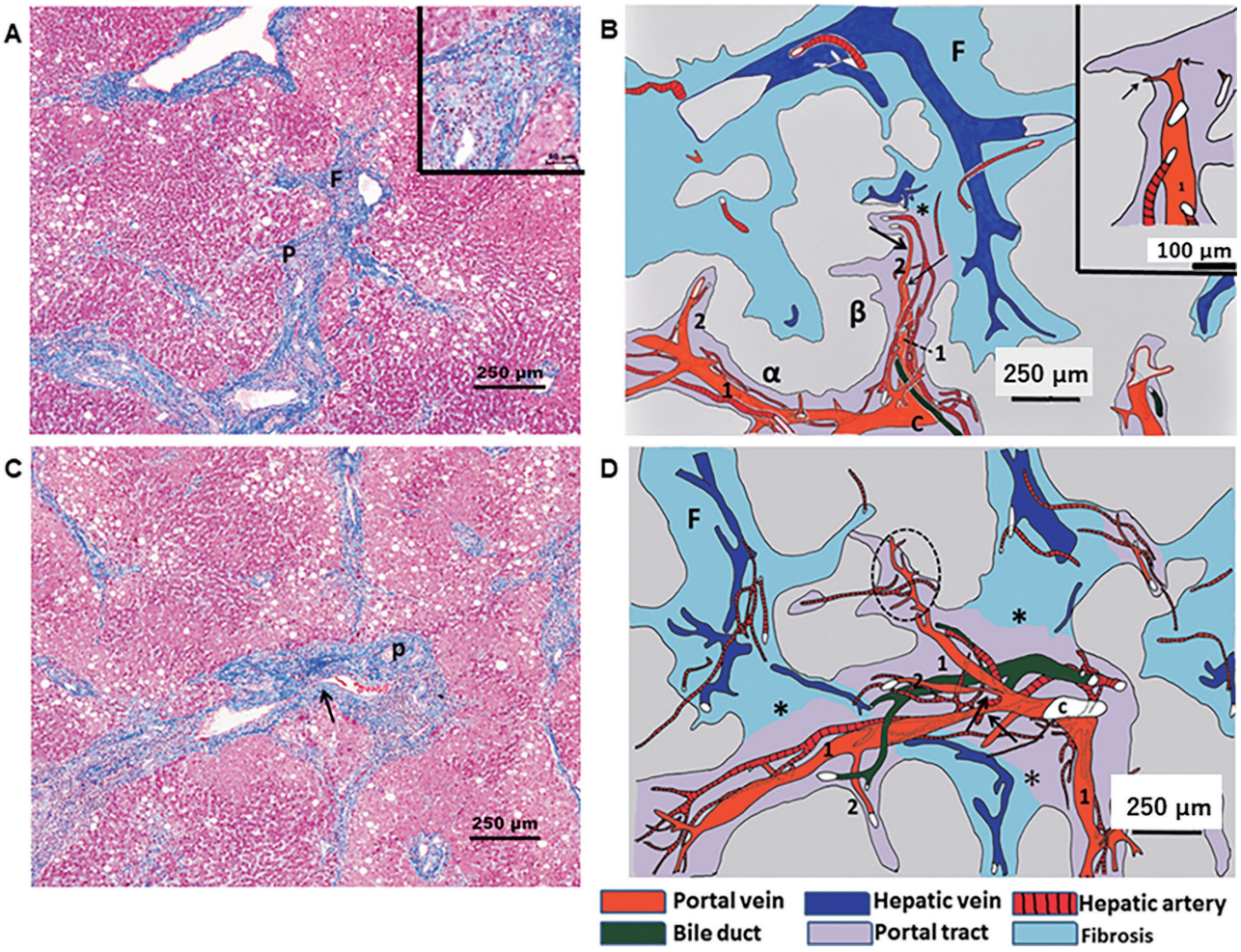

Fig. 5. Histology and histologic reconstruction of the specimens from patient 2. A : Photomicrograph of the reconstructed area shown in B. The portal tracts (P) are irregularly enlarged with fibrosis and are connected to the mildly inflamed fibrotic region (F) around the hepatic vein. Inset : Photomicrograph at a higher magnification shows a mildly inflamed portal tract with portal vein stenosis. (Masson's trichrome). B : Histologic reconstruction of the second lesion. Portal tract β is irregularly enlarged and connected broadly to the fibrotic region around the sublobular and central veins (asterisk). Narrowing of the second step branches (2) is present and runs a long distance to the distal portal tract accompanying the artery (thick arrow). The first step branch is stenosed and abruptly disrupted (thin arrow). The portal angioarchitecture is mostly preserved in the left-sided portal tract α. Inset : Further detailed reconstruction of the region with portal vein disruption indicated by a thin arrow in Figure 5B. The first step branch (1) is narrowed and disrupted and releases small branches (arrows). C : Photomicrograph of the reconstructed area shown in D. The portal tract (P) is mildly to moderately enlarged with moderate lymphocytic infiltration. The portal veins appear to be stenosed (arrow) (Masson's trichrome). D : Histologic reconstruction of the third region. Fibrosis (F) extends widely around the sublobular and central veins and broadly connects to the portal tracts (asterisks). Three first step branches (1) and their distal branches are distributed. Note that the first step branches (1) and the second step branches (2) exhibit stenosis (arrows) and fluctuating caliber. Distal branches of the portal vein show running course distortion (dotted-lined circle). Arterial development is conspicuous in the fibrotic area around the hepatic veins, which tends to become thicker and run irregularly. C : conducting portion.

low magnification (Fig. 4A), septum-like fibrosis involving the hepatic veins had extensively developed. The portal tracts exhibited a mild tendency toward fibrous enlargement along with inflammation and were often connected with the fibrotic region around the SCV. Mild to moderate macrovesicular steatosis and scattered ballooning cells were observed.

The histological reconstruction (Fig. 4B) was 516 μm thick (a total of 129 sections). Fibrosis around the SCV was frequently fused with other areas of fibrosis, forming a fibrous network. The portal tracts were mildly to moderately enlarged in places. The BF-PSCV was present. The portal

branches of the parenchymal portion were predominantly distributed. As indicated by the 1st-Brs giving off 2nd-Brs regularly at almost a right angle, the portal angioarchitecture was maintained as a whole. However, distortion of the branching and the course of the portal vein occurred in broad fibrotic portal regions. In particular, these lesions were a decrease of branches, an abrupt bend, and mildly curved running. The 1st-Brs of the portal vein and the corresponding hepatic veins tended to remain in a normal spatial relationship.

Three lesions with BF-PSCV were selected on the basis of the findings obtained from the low magnification reconstruction.

The first lesion was selected mainly for the same reason in patient 1. Histological features of the first reconstruction (Fig. 4C) included a mildly fibrous, enlarged portal tract connected with the expansive fibrotic region around the hepatic veins with narrow BF. Mild lymphocytic infiltration was present in both regions. The histological reconstruction was 266 μm thick (a total of 76 sections) and comprised an entire thickness of the BF (Fig. 4D). Two BF-PSCVs and BF between the fibrotic regions around the SCV (γ) were clearly seen. In portal tract α, small branches that emerged from the 2nd-Br ran irregularly and were arranged in a disordered manner and showed stenosis. Owing to this complication, matching these small branches with a normal branching pattern became difficult. Therefore, I considered referring to them as the equivalent of a 3rd-Br to be suitable. Arteries originating from the portal tract were directed toward the fibrotic region through BF. Although the appearance of BF-PSCV in patient 2 was similar to that in patient 1, portal vein damage had occurred in patient 2. The portal veins in portal tract β exhibited less damage than those in portal tract α. Spatial disarrangement was observed in the distal branches of the hepatic vein involved in the fibrotic area. Particularly, the distal branches ramified irregularly and curved and ran in close proximity.

Microscopic features of the second reconstructed lesion (Fig. 5A) were that the portal tract was mildly and irregularly enlarged with fibrosis and was connected with the fibrotic region around the hepatic veins. Mild lymphocytic infiltration was present in these lesions (Fig. 5A). The histological reconstruction was 220 μm thick (a total of 55 sections) (Fig. 5B). Extensive fibrosis had arisen around the SCV and was broadly connected with the portal tract. This broad BF-PSCV was a significant finding related to disease progression. In the portal tracts, two 1st-Brs ramified from the conducting portion of the portal vein and ran to the left or upward and branched. The left-sided portal tract (α) revealed that the angioarchitecture of the portal vein was almost completely preserved. Compared with portal tract α, the right-sided portal tract (β) exhibited a conspicuous distortion of the branching pattern of the portal vein. The 2nd-Br was of small caliber, which suggests narrowing, and had traveled a long distance without any branching to the distal region of the portal tract. The 1st-Br appeared to have been abruptly disrupted in its course. A more detailed reconstruction of the disrupted 1st-Br of 60 μm in thickness (a total of 15 sections) (Fig. 5B) showed that 1st-Br was stenosed and then disrupted, giving off 2 small branches that were equivalent to 3rd-Brs. These findings indicate apparent damage to the portal veins.

The third lesion with BF-PSCV was selected for histologic reconstruction because the portal tracts exhibited inflammation that was more severe than average. Histological features of the reconstructed lesion (Fig. 5C) were that the portal tracts were mildly to moderately enlarged with moderate lymphocytic infiltration. The portal veins exhibited apparent stenosis. Fibrosis developed around the hepatic veins. The histological reconstruction was 344 μm thick (a total of 86 sections) (Fig. 5D). Broad BF-PSCV was present in the 3 regions. These findings of fibrosis around the SCV were similar to those of the previous reconstructions. Three 1st-Brs had emerged from the terminal branch of the portal conducting portion. Although the branching pattern was largely preserved, close observation revealed changes that were suggestive of portal vein damage : first, 1st-Brs and 2nd-Brs exhibited varying severity of stenosis ; and second, the 2nd-Brs and 3rd-Brs exhibited running course distortion. The 2nd-Brs and 3rd-Brs were mildly tortuous and sometimes ran in the abnormal direction.

DISCUSSION

The main aim of the present study was to clarify the early and consecutive morphogenetic process of the hepatic portal tracts and portal veins involved in the noncirrhotic stage of NASH. In particular, portal vein damage was investigated in connection with the problem of the architectural remodeling of the liver lobule.

Within this context, 3 lesions with narrow BF-PSCV were 3-dimensionally investigated because the portal tracts appeared to have been almost completely undamaged.

Specimens from patient 1 showed only occasional BF-PSCV, regardless of pronounced fibrosis with inflammation around the SCV. The most common site for steatosis, degeneration (ballooning), death of the liver cells, and inflammation in the early stage of NASH was the centrilobular region. Therefore, in this region fibrosis might occur as a tissue-repairing process. Although two 3-dimensionally examined portal tracts with narrow BF-PSCV exhibited mild lymphocytic infiltration, noteworthy findings were that the portal tracts themselves were rarely fibrously enlarged and that the angioarchitecture of the portal vein was almost completely maintained. The BF-PSCV of patient 2 (Fig. 4D) was similar to that of patient 1 (Fig.3B and 3D). However, the case of NASH in patient 2, because of the occurrence of portal vein damage, was apparently more advanced than that of patient 1. Aside from that, these features were considered to represent an early morphogenetic process of portal tract involvement, resulting in BF formation in NASH. These features also differed markedly in the severity of inflammation and fibrosis from lesions with portal-central BF of chronic viral hepatitis, in which severe lymphocytic inflammation and fibrous enlargement of the portal tracts are usually present. Because periportal fibrosis develops after inflammation and liver cell damage, a reasonable consideration is that fibrosis preceded by inflammation around the SCV spreads to the portal tract in NASH. Once a pathway between the regions around the SCV and the portal tract is established, the 2 regions can easily affect each other. Therefore, the early lesions were presumed to gradually advance to broad BF-PSCV depending on the duration and severity of inflammation. What is less likely is ischemia being involved in that fibrotic process.

The second problem to be solved is damage to the portal veins. Specimens from patient 2 demonstrated extensive fibrosis around the SCV and mild to moderate fibrous expansion and inflammation of the portal tracts, which were more severe than in patient 1. The BF-SCV and BF-PSCV occurred frequently. The difference in histologic findings between the patients indicates a close parallelism between the degree of portal inflammation and the progression of portal fibrosis. The histologic reconstruction at low magnification of the specimen from patient 2 suggests that the spatial branching pattern of the portal vein (except for its most distal portion) was largely maintained and that the angioarchitectural framework of the lobule was preserved. However, detailed investigation on the basis of histological reconstruction at a higher magnification clarified distinct damage to the parenchymal portion of the portal veins, including disruption, stenosis, and distortion of their course.

On the basis of these findings, 2 considerations were identified with respect to portal vein damage. The first consideration involves lobular restructuring of the liver. What can be conceived is that the exacerbation of such portal vein damage leads to distortion of the portal vein skeleton of the liver lobule, inducing disorganization of the lobular architecture, and finally results in the development of liver cirrhosis. The same has also been described in viral hepatitis[16,17]. Therefore, portal vein damage is thought to be a critical event in terms of lobular restructuring.

The second consideration is related to the major factor damaging the portal veins. In patient 1, although the portal tracts occasionally showed mild inflammation and fibrosis, the lobular angioarchitecture was largely preserved. In contrast, the inflammation, portal fibrosis, and damage to the portal veins were more severe in patient 2 than in patient 1, indicating a strong correlation between inflammation and portal vein damage. This correlation suggests that inflammation is a key histologic process that affects the entire progression of NASH.

Regarding the involvement of inflammation, Brunt et al.[18] found via statistical analysis that the more progressed inflammation is correlated with advanced fibrosis, including BF or liver cirrhosis. Furthermore, Gadd et al. reported that early macrophage infiltration and subsequent portal inflammation are key features in the progression of nonalcoholic fatty liver disease[19].

Finally, considerations are given to fibrosis around the SCV and arterial development in NASH. In terms of fibrosis around the SCV, fibrosis around the sublobular veins was considered to have been caused by fibrosis developing and growing together around the small veins, which had emerged directly from the sublobular vein. In advanced cases of NASH, the fibrous network is formed by linkage of fibrotic lesions around the SCV[13]. Arteries markedly develop in the fibrotic region around the SCV and clearly originate from preexisting arteries in the portal tracts[13]. Arteries and CD34-positive microvessels have been identified by Gill et

al.[20] in the centrizonal region. The authors also state that the finding of centrizonal arteries in early-stage disease supports the idea that such arteries appear in or near the centrizonal region even before bridging fibrosis develops[20]. They also stressed that careful histological examination is needed to avoid mistaking the central zone for a portal zone. The precise reason for arterial development remains unknown. However, the oxygen demand of tissue increases where arteries develop. This increase suggests that in such areas stellate cells, myofibroblasts, and fibroblasts proliferate while producing extracellular matrix and consuming oxygen.

In summary, the spread of inflammation and fibrosis around the SCV is believed to cause portal tract involvement in NASH, followed by BF and damage to the portal veins. Inflammation might play a key role in disease progression. Further studies should focus on the distortion of lobular architecture in a more advanced stage.

ACKNOWLEDGMENTS

I would like to thank the staff of the Department of Pathology, The Jikei University School Medicine for their technical assistance.

Authors have no conflict of interest.

REFERENCES

1. Ludwig J, Viggiano TR, McGill DB, Ott BJ. Nonalcoholic steatohepatitis. Mayo Clinic experiences with a hitherto unnamed disease. Mayo Clin Proc. 1980 ; 55 : 434-8.
2. Brunt EM, Janney CG, Di Bisceglie AM, Neuschwander-Tetri BA, Bacon BR. Nonalcoholic steatohepatitis : A proposal for grading and staging the histologic lesions. Am J Gastroenterol. 1999 ; 94 : 2467-74.
3. Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology. 2005 ; 41 : 1313-21.
4. Bedossa P, Poitou C, Veyrie N, Bouillot J-L, Basdevant A, Paradis V, et al. Histopathological algorithm and scoring system for evaluation of liver lesions in morbidly obese patients. Hepatology. 2012 ; 56 : 1751-9.
5. Powell EE, Cooksley WG, Hanson R, Searle J, Halliday JW, Powell LW. The natural history of nonalcoholic steatohepatitis : a follow-up study of forty-two patients for up to 21 years. Hepatology. 1990 ; 11 : 74-80.
6. Ludwig J, McGill DB, Lindor KD. Review : Nonalcoholic steatohepatitis. J Gastroenterol Hepatol. 1997 ; 12 : 398-403.
7. McCullough AJ. Update on nonalcoholic fatty liver disease. J Clin Gastroenterol. 2002 ; 34 ; 255-62.
8. Lefkowitch JH, Morawski JL. Late nonalcoholic fatty liver disease with cirrhosis : a pathologic case of lost or mistaken identity. Semin Liver Dis. 2012 ; 32 : 92-8.
9. Younossi ZM. Non-alcoholic fatty liver disease - A global public health respective. J Hepatol. 2019 ; 70 : 531-44.
10. Popper H, Elias H, Petty DE. Vascular pattern of the cirrhotic liver. Am J Clin Pathol. 1952 ; 22 : 717-29.
11. Mittra SK. Hepatic vascular changes in human and experimental cirrhosis. J Pathol Bacteriol. 1966 ; 92 : 405-14.
12. Popper H. Pathologic aspects of cirrhosis : a review. Am. J Pathol. 1977 ; 87 : 228-64.
13. Hano H, Takasaki S, Kobayashi H, Koyama T, Lu T, Nagatsuma K. In the non-cirrhotic stage of nonalcoholic steatohepatitis, angioarchitecture of portal veins and lobular architecture are maintained. Virchows Arch. 2013 ; 462 : 533-40.
14. Matsumoto T, Komori R, Magara T, Ui T, Kawakami M, Tokuda T, et al. A study on the normal structure of the human liver, special reference to its angioarchitecture. Jikei Med J. 1979 ; 26 : 1-40.
15. Matsumoto T, Kawakami M. The unit-concept of hepatic parenchyma- a re-examination based on angioarchitectural studies. Acta Pathol Jpn. 1982 ; 32 : 285-314.
16. Hano H, Takasaki S. Three-dimensional observations on the alterations of lobular architecture in chronic hepatitis with special reference to its angioarchitecture for a better understanding of the formal pathogenesis of liver cirrhosis. Virchows Arch. 2003 ; 443 : 655-63.
17. Hano H, Takasaki S, Endo Y, Harada T, Komine K, Koike Y. Histological reassessment of the role of bridging fibrosis in the angioarchitectural features associated with lobular distortion of the liver in chronic viral hepatitis. Hepatology Res. 2016 ; 46 : E70-8.
18. Brunt EM, Kleiner DE, Wilson LA, Unalp A, Behling CE, Lavine JE, et al. Portal chronic inflammation in nonalcoholic fatty liver disease (NAFLD) : a histologic marker of advanced NAFLD-clinicopathologic correlations from the nonalcoholic steatohepatitis Clinical Research Network. Hepatology. 2009 ; 49 : 809-20.
19. Gadd VL, Skoien R, Powell EE, Fagaen KJ, Winterford C, Horsfall L, et al. The portal inflammatory infiltrate and ductular reaction in human nonalcoholic fatty liver disease. Hepatology. 2014 ; 59 : 1393-405.
20. Gill RM, Belt P, Wilson L, Bass NM, Ferrell LD. Centrizonal arteries and microvessels in nonalcoholic steatohepatitis. Am J Surg Pathol. 2011 ; 35 : 1400-4.