Pathological Diagnosis of Benign Hepatocellular Nodular Lesions Based on the New World Health Organization Classification

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Introduction

There are various types of benign hepatocellular nodular lesions, and their diagnostic criteria were formulated in detail. However, in 2010, the new World Health Organization (WHO) classification introduced immunohistochemical diagnostic criteria for hepatocellular adenoma (HCA) reflecting molecular pathological properties, and HCA was classified into 4 subtypes. These criteria were useful for its differential diagnosis from focal nodular hyperplasia (FNH). They were also useful for the diagnosis of HCA, its subtyping, and differentiation from FNH in Japan. However, the new WHO classification is based on principles that differ from those of conventional definitions of disease concepts and methods for the differential diagnosis. Therefore, it has caused disagreements in the diagnosis in some cases. Based on this background, we present a new perspective on the diagnosis of benign hepatocellular nodular lesions.

Abstract

There are various types of benign hepatocellular nodular lesions, and their diagnostic criteria were formulated in detail. However, in 2010, the new World Health Organization (WHO) classification introduced immunohistochemical diagnostic criteria for hepatocellular adenoma (HCA) reflecting molecular pathological properties, and HCA was classified into 4 subtypes. These criteria were useful for its differential diagnosis from focal nodular hyperplasia (FNH). They were also useful for the diagnosis of HCA, its subtyping, and differentiation from FNH in Japan. However, the new WHO classification is based on principles that differ from those of conventional definitions. Therefore, it has caused disagreements in the diagnosis in some cases. Based on this background, we present a new perspective on the diagnosis of benign hepatocellular nodular lesions.

Key Words

Benign hepatocellular nodule · New World Health Organization classification · Hepatocellular adenoma · Focal nodular hyperplasia · Nodular regenerative hyperplasia
Table 1. Classification of various benign hepatocellular nodular lesions (cited from [13] with modification)

<table>
<thead>
<tr>
<th></th>
<th>HCA</th>
<th>FNH</th>
<th>NRH</th>
<th>PNT</th>
<th>IPH</th>
<th>LRN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concept</td>
<td>Benign hepatocellular neoplasm</td>
<td>Hyperplastic nodule with central scar</td>
<td>Regenerative/ hyperplastic nodules are formed diffusely in the liver. No fibrous septa are observed.</td>
<td>Hyperplastic nodules of the hilar region often accompanied by portal hypertension.</td>
<td>Noncirrhotic portal hypertension fulfilling detailed diagnostic criteria for IPH.</td>
<td>Varies in the definition. A large regenerative nodule observed in cirrhotic liver by the Japanese General Rules for Clinical and Pathological Studies of Liver Cancer. Noncirrhotic nodules are also included in the International Working Party Classification.</td>
</tr>
<tr>
<td>Sites of nodules</td>
<td>Anywhere in the liver but frequently in the periphery</td>
<td>Diffusely present over the whole liver</td>
<td>Hilar region</td>
<td>Conceptually, a diffuse disease, but there are reports of nodule formation.</td>
<td>Anywhere in the liver</td>
<td></td>
</tr>
<tr>
<td>Number and size of nodules</td>
<td>Single/(multiple) A few centimeters</td>
<td>Multiple Many are ≤1.5 cm</td>
<td>Single/(multiple) A few centimeters (occasionally occupies 2/3 of the liver)</td>
<td>Single/(multiple) From several millimeters to a few centimeters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coexistence with portal hypertension</td>
<td>Rare</td>
<td>Infrequent</td>
<td>Frequent</td>
<td>Frequent</td>
<td>Always</td>
<td>Varies with definition</td>
</tr>
<tr>
<td>Coexistence with cirrhosis</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Varies in the definition</td>
</tr>
<tr>
<td>Problems</td>
<td>– Not so often related to oral contraceptives in Japan as reported in Western countries.</td>
<td>– Differentiation from FNH may pose a problem, particularly in patients showing central scar-like tissue.</td>
<td>– A benign tumoral lesion but may be difficult to differentiate from hyperplasia.</td>
<td>– Although a hyperplastic lesion, it may be difficult to differentiate from HCA, a benign neoplastic lesion.</td>
<td>– Extraneural areas are considered nearly normal, but there may be NRH-like or IPH-like lesions.</td>
<td>– There may be large coexisting nodules, which may be HCA- or FNH-like.</td>
</tr>
</tbody>
</table>

Detailed disease concepts, definitions and methods for the differential diagnosis have been developed for various types of benign hepatocellular nodular lesions [1–16]. They have been applied effectively so far. Recently, however, the molecular pathological properties of HCA have been clarified, primarily by a French group, and immunohistochemical diagnostic methods reflecting these findings have been introduced [17–19]. They were truly excellent works. As a result, the 2010 WHO classification clearly described these diagnostic methods and disease types of HCA [20]. Thereafter, the diagnostic methods were also introduced to Japan. Attempts to discriminate benign hepatocellular nodular lesions and to discriminate them, particularly from FNH, have begun. However, the diagnoses based on these immunohistochemical criteria have not always agreed with those based on conventional diagnostic criteria for HCA or FNH. In addition, benign hepatocellular nodular lesions include not only HCA and FNH but also various other nodular lesions. Therefore, lesions that are difficult to diagnose definitively have increased, causing considerable difficulties in daily practice.

In this article, we describe conventional disease concepts and definitions of benign hepatocellular nodular lesions, diagnostic methods, and their changes. In addition, new diagnostic criteria are explained, and their new problems and measures to utilize them are discussed.

Conventional Classification and Diagnostic Criteria for Benign Hepatocellular Nodular Lesions

Benign hepatocellular nodular lesions have been classified in detail according to clinical data, state of the background liver, and gross and histological findings of the nodules (tables 1, 2; fig. 1) [1–16]. Among these lesions, HCA is a benign neoplastic lesion [1, 2], and the large regenerative nodule (LRN) is a large nodule observed in liver cirrhosis [10]. In the International Working Party (IWP) classification, various nontypical le-
sions of noncirrhotic benign hepatocellular nodules are also lumped together as LRN [10]. By the way, FNH [3, 4], nodular regenerative hyperplasia (NRH) [5, 6], partial nodular transformation (PNT) [7], and benign hepatocellular nodular lesions observed in idiopathic portal hypertension (IPH) [8, 9] are the lesions comprehensively called hepatocellular nodules caused by abnormal intrahepatic circulation. Presently, there are two concepts about FNH, NRH, PNT, and nodules in IPH. One is the conventional concept, namely, these are diseases caused by different etiological mechanisms: FNH is a hyperplastic lesion due to vascular malformation, NRH is characterized by small intrahepatic nodules formed by a compensatory regenerative mechanism induced primarily by secondary vascular disorders such as thrombosis and vasculitis, and IPH, the etiology of which remains unclear, is regarded as a lesion of a different entity [1–10]. According to the other concept, these lesions are different subtypes or variants of the same disease with transitional or intermediate types [11–13]. Their common cause is considered as vascular malformation [11–13].

The second concept was formulated to solve the various problems with the conventional concepts as shown in table 1. We encountered various difficult lesions when we used only the traditional concept. In the second concept, these lesions are considered analogous diseases forming the category of benign hepatocellular nodules caused by a common etiological mechanism, which is an anomaly of the components of the portal tract. Although the size and distribution of the nodular lesions are various, their interstitia, namely the portal tracts, show very similar features (fig. 2).

### Table 2. Differential diagnosis of HCA and FNH (cited from [15])

<table>
<thead>
<tr>
<th></th>
<th>FNH</th>
<th>HCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Hyperplastic lesion caused by vascular malformation</td>
<td>Benign neoplastic lesion</td>
</tr>
<tr>
<td>Background liver</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Gross characteristics</td>
<td>Central scar (+)</td>
<td>Central scar (–)</td>
</tr>
<tr>
<td>Histological characteristics</td>
<td>Anomalous blood vessels, anomalous portal tract</td>
<td>Portal tract (–)</td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td>Associated with oral contraceptives (?)</td>
<td>Associations with oral contraceptives, anabolic steroid hormone, glycogen storage disease, etc.</td>
</tr>
<tr>
<td></td>
<td>Malignant transformation (–), hemorrhage (–)</td>
<td>Malignant transformation (+), hemorrhage (+)</td>
</tr>
</tbody>
</table>

Fig. 1. Gross images of typical and nontypical benign hepatocellular nodular lesions (cited from [12, 13, 15] with modification).

- **a**: FNH: a stellate central scar is clearly seen.
- **b**: HCA: no central scar present. In both **a** and **b**, the background liver is normal.
- **c**: NRH: while small nodules are distributed diffusely over the entire liver, no fibrous septa such as those in liver cirrhosis are noted.
- **d**: A nontypical nodule is shown in this cross section of the liver shown in **c**. The background liver shows characteristics of NRH. The nodule indicated by the black arrow shows a clear central scar and closely resembles FNH. However, as the background liver is not normal, the lesion is not diagnosed as FNH according to the conventional definition. The nodule indicated by the white arrow cannot be definitively diagnosed because there is no central scar. Unlike FNH, the diameter is too large for NRH, and, while it resembles HCA, there is no history of the use of oral contraceptives.
These lesions are called anomalous portal tract syndrome (fig. 3a) [12], and this concept is useful for the interpretation of various nontypical cases. It is also useful for the evaluation of their relationships with hemangiomas of the liver, portal hypertension, congenital hepatic fibrosis, and bile duct malformation (fig. 2, 3). Nontypical cases with hepatocellular hemangiomatous lesions can also be interpreted by this concept [21]. Although this concept alone may not be sufficient to explain the etiology of many lesions including IPH and NRH, it is recommended to consider this concept when we encounter various difficult cases [22]. Recently, the original concept (fig. 3a) has been revised (fig. 3b) owing to the development of the WHO classification. It is explained later in this study.

At any rate, benign hepatocellular nodular lesions were conventionally classified into benign neoplastic lesions, various nonneoplastic nodules associated with abnormal circulation, and regenerative nodules in liver cirrhosis (table 1).

**Diagnosis of HCA Based on the New WHO Classification and Its Differentiation from FNH**

Recently, however, the 2010 WHO Classification of the Tumours of the Digestive System has been published, and HCA was classified into 4 subtypes based on the genotype [20]: (1) hepatocyte nuclear factor 1α (HNF1α) inactivated type (H-HCA), (2) β-catenin activated type (b-
HCA), (3) inflammatory HCA (I-HCA), and (4) the unclassifiable type (u-HCA). Points of differentiation from FNH were also specified (table 3, fig. 4). It is indeed a great advance in hepatology.

Concerning these 4 subtypes, the mutant gene, immunohistochemical findings reflecting the mutations, gender difference, histological characteristics, and characteristic clinical findings have been clarified: (1) H-HCA is characterized by inactivation of HNF1α, immunohistochemically, by a decrease in liver fatty acid-binding protein (L-FABP), a predominance in women, and, histologically, fatty degeneration (fig. 4a, b) and is suggested to be related to oral contraceptives. (2) b-HCA is characterized by activation of β-catenin, immunohistochemically, intranuclear accumulation of β-catenin or diffuse positivity for glutamine synthetase (GS), a predominance in women, and, histologically, cellular atypia and is associated with a high risk of carcinogenesis (however, nuclear atypia was rare in the Japanese cases reported) (fig. 4c–e). (3) I-HCA is characterized by mutations of genes such as gp130, STAT3, and GNAS, immunohistochemically, by positivity for serum amyloid A (SAA) and C-reactive protein, and, histologically, inflammatory cell infiltration, ductular reactions, and sinusoid dilation and is considered to be closely related to drinking and obesity (fig. 4f, g). (4) u-HCA lacks gene mutations or immunohistochemical findings, but is diagnosed as HCA from gross and histological findings. FNH shows no gene mutations or immunohistochemical characteristics described in (1) to (3), but is characterized immunohistochemically by a

Fig. 3. Concept of anomalous portal tract syndrome (cited from [12, 13, 14] with modification). a The original concept is presented: various lesions are caused by congenital anomaly of the portal tract. Abnormal vasculature due to malformation causes various types of abnormal circulation, and in addition, it causes various types of hyperplastic hepatocellular nodular lesions. Hemangioma and various types of bile duct malformation sometimes coexist with these hepatocellular nodules because both blood vessels and bile ducts are components of the portal tract. b Revised concept after adjusting for the new WHO classification. The revised concept presumes the three stages in every lesion, i.e. nonmutated, focally mutated and entirely mutated stages.
map-like distribution of GS (fig. 4h). It is also reported to show a central scar, inflammatory cell infiltration, ductular reaction, and sinusoid dilation as characteristic features. However, as FNH occasionally shows no central scar, and as inflammatory cell infiltration, ductular reaction as well as sinusoid dilation are also observed in I-HCA, the map-like distribution of GS is useful for its diagnosis.

Results in Japan

The new diagnostic methods and histological and clinical findings observed above have been documented primarily by a French group [17–20]. Although they are excellent works, we had to examine whether or not these findings are directly applicable to Japanese patients. Race and clinical background are quite different between Japan and Europe. In Japan, there have been reports by Sasaki et al. [23, 24] and Soejima et al. [25].

Soejima et al. [25] evaluated 35 nodules of HCA in 26 patients (examined by surgery in 23, autopsy in 2, and biopsy in 1) consisting of 13 males and 13 females. None of them took oral contraceptives, and only 1 of them had glycogen storage disease. The clinical background of HCA in these Japanese patients markedly differed from that observed in reports from Western countries. However, 2 patients showed congenital absence of the portal vein, 1 showed IPH, 4 had complicating FNH, and a considerable number of patients showed abnormal intrahepatic circulation. These lesions have been conventionally classified as hyperplastic lesions caused by abnormal circulation or FNH-like lesions.

In addition, of the 35 HCA nodules, 11 (31%) were classified by immunostaining as H-HCA, 7 (20%) as b-HCA, 10 (29%) as I-HCA, and 7 (20%) as u-HCA. These percentages were similar to those in Western populations despite differences in clinical background. Their work did not include patients with alcoholic abuse or viral cirrhosis.

Moreover, the expression of OATP1B3 in various subtypes was analyzed by immunostaining. It was attenuated in 6 of 8 (75%) of the H-HCAs, 0 of 6 (0%) of the b-HCAs, 9 of 10 (90%) of the I-HCAs, and 4 of 6 (67%) of the u-HCAs, compared with nonnodular areas. Five nodules were excluded from the study because their stainability was difficult to evaluate. The expression was frequently attenuated in H-HCA and I-HCA, but not in b-HCA. In addition, the OATP1B3 expression was maintained or enhanced in all 8 nodules that showed intranuclear accumulation of β-catenin (6 nodules of b-HCA and 2 nodules of H-HCA). This indicates a close relationship between HCA subtypes (β-catenin gene mutation) and the OATP1B3 expression, as in hepatocellular carcinoma (HCC) [26].

Table 3. Characteristics of HCA subtypes and FNH (cited from [15])

<table>
<thead>
<tr>
<th></th>
<th>H-HCA</th>
<th>b-HCA</th>
<th>I-HCA</th>
<th>u-HCA</th>
<th>FNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene mutations</td>
<td>HNF1α</td>
<td>β-catenin</td>
<td>gp130, STAT3, GNAS</td>
<td>positive for GS, nucleus positive for β-catenin</td>
<td>positive for SAA positive for CRP</td>
</tr>
<tr>
<td>Immunostaining</td>
<td>attenuation of L-FABP</td>
<td>positive for GS, nucleus positive for β-catenin</td>
<td>positive for SAA positive for CRP</td>
<td>map-like GS distribution</td>
<td></td>
</tr>
<tr>
<td>Gender difference</td>
<td>predominant in women</td>
<td>predominant in women</td>
<td>predominant in women</td>
<td>predominant in women</td>
<td>predominant in women</td>
</tr>
<tr>
<td>Histological features</td>
<td>fatty degeneration</td>
<td>cell atypia</td>
<td>inflammatory cell infiltration, ductular reaction, sinusoid dilation</td>
<td>central scar, abnormal vasculature, ductular reaction, sinusoid dilation</td>
<td></td>
</tr>
<tr>
<td>Characteristic clinical findings</td>
<td>oral contraceptives</td>
<td>oral contraceptives</td>
<td>drinking, obesity</td>
<td>central scar, abnormal vasculature demonstrated by imaging</td>
<td></td>
</tr>
<tr>
<td>Frequency in all adenoma patients</td>
<td>35 – 40%</td>
<td>10 – 15%</td>
<td>45 – 60%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Possibility of hemorrhage</td>
<td>(+)?</td>
<td>(+) frequent!</td>
<td>(+)?</td>
<td>(+)?</td>
<td></td>
</tr>
<tr>
<td>Possibility of cancerration</td>
<td>(+)?</td>
<td>(+) frequent!</td>
<td>(+)?</td>
<td>(+)?</td>
<td></td>
</tr>
</tbody>
</table>

For figure see next page.
Furthermore, when correlations between OATP1B3 expression and gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid MRI (EOB-MRI) findings \[27, 28\] were evaluated in 10 HCA nodules in 7 patients, the 8 nodules that showed attenuation of OATP1B3 expression were hypointense in the hepatocyte phase of EOB-MRI, and 1 nodule with intranuclear accumulation of β-catenin was isointense, showing a significant association in 9 (90%) of the 10 nodules. This suggests that HCA accompanied by intranuclear accumulation of β-catenin, such as b-HCA, which is reportedly at high risk of canceration \[29\], may be diagnosed by EOB-MRI. However, atypia was not significant in b-HCA in our patients, unlike in reports from Western countries. Additionally, the risk of malignant transformation of b-HCA needs to be evaluated further in a greater number of Japanese patients.

Usefulness and Problems of the New WHO Classification

The new WHO classification has reached an epoch-making progress. However, its usefulness and problems have to be precisely evaluated for further development.

Usefulness

When the new WHO classification incorporating knowledge about gene mutations and their immunohistochemical manifestations was applied to Japanese patients, it was confirmed to be very useful in the following respects. (1) The diagnosis of HCA was facilitated by evidence obtained by simple procedures of immunohistochemistry. (2) Each subtype was found to have characteristic histological features, genotype, and immunostaining findings, and they were useful for the imaging diagnosis and for predicting prognosis.

Problems

However, in interpreting the various lesions practically, the new WHO classification has the following problems. (i) There exist differences and contradictions compared with the conventional diagnostic criteria. (ii) Some patients with chronic liver diseases show positive immunohistochemical findings for HCA (HCA-like lesions with an abnormal background liver). (iii) Some lesions show immunohistochemically focal positive areas.

Differences and Contradictions Compared with the Conventional Diagnostic Criteria

Figure 5 shows a macroscopical FNH-like lesion that exhibited immunohistochemical findings of H-HCA \[30\]. A nodule of 2 cm in diameter was detected, which contained a thick portal tract and showed a structure resembling a central scar. In a high magnification view, the 3 elements of the portal tract, i.e., the artery (a), portal vein (p), and bile duct (b), are clearly observed. These findings widely deviate from the conventional diagnostic criteria for HCA. In addition, the patient showed abnormal intrahepatic circulation (i.e., congenital absence of the portal vein) in the background liver. The images suggested FNH rather than HCA. However, on L-FABP immunostaining, this nodule showed clear attenuation of staining compared with the background liver, and a diagnosis of H-HCA was made.
HCA-Like Lesions with an Abnormal Background Liver

Figure 6 shows a nodular lesion of 1.5 cm in diameter detected in a patient with alcoholic liver cirrhosis [24]. In this nodule, the presence of a central scar suggestive of FNH is grossly clear. However, on immunostaining, SAA was clearly positive, and the lesion was diagnosed as a nodule with properties similar to those of I-HCA. However, according to the conventional diagnostic criteria, HCA is considered to occur in the normal liver. If these criteria are strictly applied, the lesion cannot be definitively diagnosed as I-HCA and is inevitably classified as an SAA-positive nodule present in a liver with alcoholic cirrhosis. In addition, nodular lesions in heavy drinkers have been reported to show characteristics resembling those of FNH [31, 32]. In this respect, the diagnosis as HCA in this lesion contradicts with the past reports [31, 32].

Presence of Focal Positive Areas

Figure 7a shows a macroscopic finding of a nodule with focal SAA-positive areas. Figure 7b is a panoramic view of the SAA immunostaining, showing foci of positive staining in the nodule. This lesion was found in the same patient as the one shown in figure 6 [24]. This patient had 7 benign hepatocellular lesions, of which 3 were diffusely SAA positive, 2 were partially SAA positive, and 2 were SAA negative. The coexistence of nodules that exhibit different staining properties in the same liver suggests that SAA-positive foci may appear in SAA-negative nodules and spread further to all nodules. It also poses a new question about how nodules showing focal SAA positivity should be definitively diagnosed. In our experience, it is not rare that SAA-positive foci are found in nodules. It has already been reported that SAA-positive microfoci are also present in the background liver [33]. Further evaluation is necessary to determine whether these focal SAA-positive areas are microfoci or evidence of the development of a neoplastic nodule (HCA) from a nonneoplastic nodule (FNH). A report has been published describing that HCA foci appeared in nodules of FNH [34]. We have also encountered another patient in whom SAA-positive and GS-attenuated I-HCA-like areas appeared in SAA-negative FNH-like nodules showing a map-like GS staining pattern [35].
Discussion on Difficult-to-Diagnose Lesions and Definitive Diagnosis of Individual Lesions

With the advent of the new WHO classification, the diagnosis of benign hepatocellular nodular lesions has entered a new era. However, the classification often contradicts the conventional diagnostic criteria, and considerable numbers of lesions are difficult to definitively diagnose. We should discuss how to cope with such difficult cases.

Characteristics and Problems of the Conventional Diagnostic Criteria and New WHO Classification

First, the characteristics of and problems with the conventional diagnostic criteria and new WHO classification are reviewed (table 4). According to the conventional diagnostic criteria, as shown in table 2, the diagnosis is made by inferring a specific disease state, clinically, from HCA-related background factors (oral contraceptives, glycogen storage disease, etc.) and, pathologically, from characteristic gross and histological features. Its problems include the following: (1) there are no molecular biological grounds for regarding lesions as neoplasms, (2) occasionally difficult to differentiate clearly from nonneoplastic lesions such as FNH and from well-differentiated HCC, and (3) nontypical cases increase if definitions are strictly applied.

On the contrary, according to the new WHO criteria, diagnoses are made by demonstrating various gene mutations using molecular techniques or based on immunohistochemical findings, which are their indirect evidence. Its problems include the following: (1) the diagnoses are not necessarily consistent with those based on the conventional criteria, (2) gene mutation itself is not necessarily the definite evidence of the neoplastic nature, and (3) lesions showing multiple gene mutation patterns are difficult to subclassify.

Reevaluation of Disease Concepts

To solve such problems, adjustment between the conventional disease concepts and the new WHO classification is necessary. As mentioned above, some lesions showing HCA-related gene mutations and immunohistochemical findings appear to deviate considerably from the conventional disease concept of HCA. Lesions in males, those with no HCA-related clinical background, such as the use of oral contraceptives, nodules containing an abnormally thick portal tract, and those closely resembling FNH with a clear central scar are examples. The new WHO classification is considered to be a method to directly and indirectly demonstrate gene mutations of hepatocytes, rather than digging out latent HCA consistent with the conventional disease concept. In addition, HCA and FNH are not the only benign hepatocellular nodular lesions, which vary widely, as shown in table 1 and figure 3. Since there are also SAA-positive foci in the nonnodular background liver [33], theoretically, gene mutations may occur in each lesion presented in table 1. Indeed, the background liver had congenital absence of the portal vein in the patient shown in figure 5. This vascular anomaly suggested that the nodule was a hyperplastic nodule caused by circulatory abnormality (FNH-like lesion) ac-

Table 4. Characteristics and problems of the conventional diagnostic criteria for HCA and the new WHO classification

<table>
<thead>
<tr>
<th>(A)</th>
<th>Conventional diagnostic criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
<td>Diagnosed by inferring a specific disease state, clinically, from HCA-related background factors (oral contraceptives, glycogen storage disease, etc.) and, pathologically, from characteristic gross and histological features.</td>
</tr>
<tr>
<td>Problems</td>
<td>(1) No molecular biological evidence for being a neoplasm.</td>
</tr>
<tr>
<td></td>
<td>(2) Occasionally difficult to differentiate clearly from nonneoplastic lesions such as FNH and from well-differentiated HCC.</td>
</tr>
<tr>
<td></td>
<td>(3) Nontypical cases increase if definitions are strictly applied.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(B)</th>
<th>Diagnostic criteria of the new WHO classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
<td>Diagnosed based on gene mutations of hepatocytes or immunohistochemical findings, which are their indirect evidence.</td>
</tr>
<tr>
<td>Problems</td>
<td>(1) The diagnoses are not necessarily consistent with those based on the conventional criteria.</td>
</tr>
<tr>
<td></td>
<td>(2) Gene mutation itself is not necessarily the definite evidence of the neoplastic nature.</td>
</tr>
<tr>
<td></td>
<td>(3) Lesions showing multiple gene mutation patterns are difficult to subclassify.</td>
</tr>
</tbody>
</table>
According to the conventional concepts. The background liver in the patients presented in figures 6 and 7 showed alcoholic cirrhosis. Therefore, the differential diagnoses of these nodules (particularly the nodule with no clear central scar shown in fig. 7) are considered to include LRN- as well as FNH-like lesions.

Reevaluation of the Classification of Disease Entities Based on Clinical Data and Histological Findings in the Background Liver

Classifying typical features of diseases in detail is useful to some extent for understanding the diseases and their differential diagnosis. However, if such a classification is applied with excessive rigidity, nontypical lesions increase, making the definitive diagnosis difficult. The definition that the background liver of HCA and FNH is normal can simply be a matter of probability. Chronic liver disease is not considered as the definite causative factor of HCA and FNH, while it is definitely related to hepatocarcinogenesis. There is no guarantee that patients with HCA or FNH are not infected by hepatitis virus or will not become heavy drinkers. In addition, not all patients with HCA have its risk factors.

Flexible thinking is important in the diagnosis and interpretation of the characteristics of each lesion.

Definitive Diagnosis of Each Lesion

Personalized Diagnosis

From the above viewpoints, a tentative proposal for the definitive diagnosis of individual patients including those with nontypical HCAs is presented (fig. 8: personalized diagnosis or the three-dimensional diagnosis).

The gross features of benign hepatocellular nodular lesions show a wide variation. They not only vary in the number of nodules, presence or absence of the capsule, and presence or absence of the central scar, but may also show incomplete patterns. In addition, in the background liver, there may be multiple clear nodules in some patients, but nodules are as obscure or difficult to recognize as nodules in others. The severity of the liver disorder also varies. Such morphological features are described in detail and mapped along the horizontal axis (x-axis). As a

Fig. 8. Concept of the personalized diagnosis (three-dimensional diagnosis) (cited from [15] with modification). The x-axis shows various gross and histological findings. The y-axis shows the degree of progress toward neoplasia and malignancy. The z-axis shows various background factors.
result, they can be classified roughly into HCA-like, FNH-like, NRH-like, and nontypical.

The presence or absence of gene mutations such as HNF1α inactivation (+), β-catenin activation (+), and gp130 mutation (+) and their accumulation is mapped along the vertical axis (y-axis). Attenuation of L-FABP (+), β-catenin (+), and SAA (+), which is indirect evidence of the above mutations, may also be used. Thus, gene mutations occurring at 2 or more loci can also be automatically indicated. There is no need to force HCAs into 4 subtypes. If different gene mutations are discovered in the future, they can also be dealt with by this method. Moreover, independently of the x- and y-axes, clinical background factors such as the history of the use of oral contraceptives, infection with hepatitis virus, IPH, and heavy alcohol intake are mapped along the z-axis. By such a combination of morphological features, gene mutations, and clinical background factors, even nontypical lesions and lesions in which various factors are involved in a complex manner can be classified.

For example, the patient with the nodule shown in figure 6 was a heavy drinker. The gross and histological findings of the nodule were compatible with FNH, but the nodule was SAA positive. A more accurate diagnosis than this is impossible.

In addition, it is necessary to evaluate the degree of progress toward neoplasia and malignancy of the nodule. Conventionally, FNH and HCA were considered benign, but HCA has been reported to show malignant transformation. However, FNH has also been reported to be malignant in 2 of more than 800 cases [36]. Moreover, as HCC arising in the normal liver is encountered not infrequently, the occurrence of precancerous lesions, namely, accumulation of various gene mutations, in FNH and various benign nodular lesions is sufficiently possible. In diagnosing various benign hepatocellular nodular lesions, we immunohistochemically examine heat shock protein 70 (HSP70) and glypican 3 (GPC3) [37] to evaluate the possibility of well-differentiated HCC and precancerous conditions, in addition to the above HCA-related immunohistochemical examinations. The histological assessment of the presence or absence of stromal invasion is also important [37, 38]. The findings of the degree of malignancy are also mapped along the y-axis.

Figure 8 presents a conceptual diagram of this classification. By following this concept, various factors should be evaluated independently for the diagnosis of individual cases (personalized diagnosis or three-dimensional diagnosis). Thus, we can discuss whether the lesion is typical or nontypical.

Revised Concept of Anomalous Portal Tract Syndrome

We would like to reemphasize the usefulness of the revised concept of anomalous portal tract syndrome (fig. 3b). Although the original concept of anomalous portal tract syndrome was useful for the various nontypical lesions, it did not include the possibility of neoplastic change (fig. 3a). Owing to the development of the WHO classification, we added the three stages of mutation, i.e. nonmutated, focally mutated and entirely mutated, to each type of the nodule. The difficult cases such as those shown in the figures 5–8 are well interpreted by this revised concept. In Japanese cases, benign hepatocellular lesions accompany abnormal hepatic vasculature more frequently than oral contraceptives. They must have been caused by abnormal hepatic circulation rather than oral contraceptives. Especially for the interpretation of these Japanese cases, this revised concept is useful.

Closing Remarks

The new WHO classification is a very useful system that has clarified various gene mutations and immunostaining findings of benign hepatocellular nodular lesions. We truly respect former studies. However, the classification is not necessarily perfect and presents some problems. We sincerely hope that this article is helpful to solve these problems.

Disclosure Statement

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