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Histology of portal vascular changes associated with idiopathic non-cirrhotic portal hypertension: nomenclature and definition.

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Abstract

Idiopathic non-cirrhotic portal hypertension (INCPH) is a rare vascular liver disease that has attained a new interest in recent years. It is characterized by clinical signs of portal hypertension in the absence of cirrhosis or severe fibrosis and any known cause of portal hypertension. Since much uncertainty exists about INCPH pathophysiology and no definite diagnostic tests are available, liver biopsy is an essential tool to achieve a definite diagnosis. Unfortunately, the histological diagnosis of INCPH is not always straightforward, since the characteristic lesions are unevenly distributed, vary greatly in their severity and are often very subtle, and not all are necessarily present in a single case. Furthermore, specifically for the characteristic portal vessel changes observed in INCPH, the terminology and definition is ambiguous, which adds complexity to the already complex clinical-pathological scenario.

An international study group of liver pathologists and hepatologists pursued a consensus on nomenclature for the portal vascular lesions of INCPH. Such standardization may assist pathologists in the recognition of such lesions and will possibly facilitate further advancement in this field.

Key words: idiopathic non cirrhotic portal hypertension; liver vascular lesions; obliterative portal venopathy; phlebosclerosis.

Introduction

Idiopathic non-cirrhotic portal hypertension (INCPH) is a vascular liver disease of unknown etiology, characterized by clinical signs of portal hypertension (PH) in the absence of rhosis[1]. Therefore, INCPH is frequently revealed by splenomegaly, thrombocytopenia, esophageal varices and/or variceal bleeding in patients with preserved liver function. The diagnosis of INCPH requires exclusion of any disorders known to cause portal hypertension in the absence of cirrhosis (e.g. infiltrative diseases, vascular malignancies, schistosomiasis, ngenital hepatic fibrosis, sarcoidosis), and other known causes of liver diseases[1,2]. variety of terms was introduced for this non-cirrhotic liver disease[1-11], such as Banti syndrome, non-cirrhotic portal fibrosis, hepatoportal sclerosis, incomplete septal cirrhosis, obliterative portal venopathy and nodular regenerative hyperplasia. After recognizing that these names appear to reflect a disease entity, albeit with heterogeneous morphological ects[7], the umbrella term INCPH was introduced to standardize the nomenclature[1]. INCPH is relatively rare, particularly in western countries, but it is probably underdiagnosed misdiagnosed, since, on clinical presentation, it closely mimics "cryptogenic cirrhosis"[8]. The lack of pathognomonic clinical and laboratory findings makes the histological examination of liver tissue samples critically important to achieve a definite diagnosis of CPH.[1,2] INCPH liver may show a variety of lesions[1-13]. The most characteristic encompass a constellation of portal-periportal vascular changes, supposedly involved in the pathogenesis. However, the histopathological diagnosis of INCPH is not always straightforward, since the characteristic lesions are unevenly distributed, vary greatly in their

severity, are often very subtle, and not all are necessarily present in an individual case[11,13]. The limited sampling obtained by liver biopsy presents further challenge in recognizing relevant histological features. Therefore, the pathologist who is not aware of the clinical background, and/or does not include INCPH in the differential diagnosis, may miss the subtle morphologic changes of this condition. The scenario is even more complicated in that it is w recognized that in cases of INCPH, vascular lesions may be seen at earlier stages, when nical signs of PH are still lacking, or even never develop or are documented[12,14,15]. Furthermore, the specificity and sensitivity of these histopathological changes is currently unknown since they can be also seen outside the context of portal hypertension in chronic nditions of different etiologies[16,17]. To add to the complexity, standard nomenclature and definition of characteristic INCPH portal lesions is lacking, which greatly contributes to problems in diagnosing this entity.

The semantic confusion clearly reflects (but also contributes to) our uncertainties surrounding the pathogenesis and clinical meaning of the observed portal vascular lesions. Clear morphological definitions and terminology will enable follow-up studies, which can determine the utility of these definitions, and their potential impact on understanding pathophysiology, and/or in guiding clinical management of the patients.

The present paper was written after a three-day meeting of the International Liver Pathology dy Group, also known as the "Elves"[18], devoted to vascular liver lesions, which was held in Padova (Italy) in 2015. We worked to arrive at a consensus on the definition and nomenclature for portal/periportal microvascular changes characteristic of INCPH, that can assist clinical and investigative pathologists in recognizing the histopathologic features and applying them in a consistent fashion, necessary for gaining a better understanding of this disease.

For the sake of thematic focus, this manuscript is not a comprehensive review of the histopathology of INCPH. Therefore, pathological entities, such as nodular regenerative hyperplasia or incomplete septal cirrhosis, known to be associated with INCPH, or common accompanying lesions (sinusoidal dilatation, terminal hepatic vein enlargement) are not considered. For a comprehensive approach to the diagnosis of INCPH, the readers are referred to available literature[11,13,19]. The goal of this paper is to recommend a system of standardized nomenclature, so as to overcome the inconsistency of current terminology used for the characteristic INCPH portal/periportal vascular changes.

Definitions and recommendations are based on what we have observed in routine liver biopsies, using routine stains (H&E and collagen stain). We use adjunctive stains for specific purposes, for example reticulin stain is useful when nodular regenerative hyperplasia is suspected in INCPH.

It is of worth emphasizing that the portal/periportal lesions not only may be variably combined in a single biopsy specimen, but different lesions may coexist in a same portal/periportal area and in some cases, it might be difficult to differentiate one from the other. Since small vascular structures are affected in INCPH, one should try to derive and construct their 3-dimensional behavior from the routine consecutive liver biopsy sections that are obtained for a liver biopsy. Besides providing a better sense of the 3-dimensional architecture of a lesion, following such lesions through all levels will help in identifying the different lesions properly. As was demonstrated by Crawford et al. in their study of normal liver biopsies[20], one-section-only may be not as informative as following findings-of-interest through the many levels of a routine liver biopsy.

Normal histology of intrahepatic portal vasculature

In normal adult liver biopsy, most portal tracts (PTs) contain portal vein, hepatic artery and bile duct profiles. Portal ‘dyads’ containing only hepatic artery and bile duct profiles, representing terminal PTs, are also commonly seen and should not be considered

hological[20,21]. The successive branches of the smaller portal veins are the preterminal portal venules, found in portal tracts of triangular cross sections, and the terminal portal venules (about 20–30 μm in diameter) surrounded by scanty connective tissue in portal tracts

circular cross sections[21]. In normal peripheral PTs, hepatic arteries and bile ducts exhibit similar diameters, whereas portal vein profiles are on average three times greater in minimum

meter and they can be up to 4 times greater[20]. Portal veins are entirely confined to the PT and connect to sinusoids through the inlet venules. These are very short side branches, which have an endothelial lining with a basement membrane and scanty adventitial fibrous

nnective tissue but no smooth muscle in their walls[20]. Inlet venules are usually not visible in normal conditions.

Portal and periportal changes in INCPH

Portal vein narrowing

In INCPH, the portal venous radicles show variable degrees of luminal narrowing,

appearance or sclerosis [1-13;19,22]. This change usually occurs in a fibrotic PT. Indeed, round

rous PT enlargement is characteristic of INCPH[23]. The percentage of portal tracts involved and the degree of fibrosis is variable. Since a normal PV branch is at least three times greater than the bile duct, comparing their caliber in the same PT may help one identify a narrowed PV (its caliber may be similar, or even smaller, to that of the bile duct). For larger portal veins, luminal narrowing may be recognized by identifying the smooth muscle fibers of the portal vein as revealing the original contour of this structure, and determining whether the

endothelial lining delineates a smaller luminal space. The endothelial lining may be highlighted by CD34 stain although obliteration of the portal vein lumen will also eliminate immunoreactive endothelial cells, The presence of a circumferential profile of smooth scle fibers without any interior lumen is a sign of luminal disappearance. Identification of narrowed portal vein in the smallest PTs may be very difficult. However, the presence of fibrosis along with an eccentrically-placed hepatic artery/bile duct pair is a helpful sign of portal vein disappearance. This histologic sign is different than identifying a true hepatic artery/bile duct "dyad", since the latter lacks fibrosis and has a delicate investment of extracellular matrix that wraps only around the hepatic artery and bile duct profiles, without any additional cross-sectional area. The overall impression of portal vein loss can also be supported by doing a "profile count" of one entire liver biopsy histologic section. With a minimum of 7 portal tract profiles that are not at the edge of the biopsy sample, "paucity" of portal veins may be appreciated. (The normal percutaneous liver biopsy has portal veins in 70% of portal tracts, inclusive of both portal tracts with portal veins/hepatic arteries/bile ducts d "dyads", with hepatic artery/bile duct pairs only)[20].

In the literature, different terms have been used to refer to this alteration, which is regarded as initial lesion of INCPH leading to increased intrahepatic resistance. Mikkelsen et al .[6] roduced the term "phlebosclerosis". Obliterative portal venopathy[2,12,24,25], portal vein iteration[7], hepato-portal sclerosis[9,26], and small portal vein obliteration[27] are other terms commonly used.

The term phlebosclerosis is misleading, since sclerosis of the PV wall is not invariably sent. Indeed, in the paper by Verheij et al.[28] phlebosclerosis was defined as "a portal vein with a reduced lumen in a fibrotic portal tract". As for the other terms, they have been differently defined and often used to refer either to the clinical syndrome or the entire ctrum of vascular changes seen in INCPH. For example, Nayak and Ramalingaswami[24],

defined obliterative portal venopathy as “scarring and obliteration of small portal vein branches along with an increased number of small vascular channels within the portal tracts and incomplete thin fibrous septa”. As emphasized above, the entire spectrum of portal vascular changes is not necessarily found in every single case of INCPH, particularly in liver biopsy samples. Furthermore, the PV is not always obliterated, its lumen may be narrowed but still visible. Therefore, a term that refers only to the portal vein branch lesion, which may be an isolated change, and a more clear definition, is advisable. We suggest to name this lesion simply PV *stenosis*. The word stenosis comes from the ancient Greek and in medicine means pathological narrowing of a lumen, which may be more or less severe and even complete.

Recommended term: PV stenosis

Definition: Incomplete or complete obliteration of portal vein branches ± thickening of the wall (Fig. 1 and Table 1).

Portal /periportal venous alterations

Portal vascular spaces directly abutting upon the hepatic parenchyma at the limiting plate is a quent finding in INCPH[9,11,13,26,29,30], giving the appearance of a prolapsed portal vein. This is thought to be rarely or never seen in normal livers. Indeed, in normal liver, a portal vein is irely confined to the PT and separated from the hepatocytes by connective tissue.[21] tsumoto, who first observed this change in liver with Banti’s syndrome[29] coined the term errant vessel”. Ohbu et al.[30] provided a detailed histopathological classification of portal vascular changes in cases of non-cirrhotic PH, and called this alteration “type II aberrant vessel” defining it as “an aberrant vessel connected to the peripheral portal vein”. However, with the term “aberrant vessels” they covered both intra- and periportal vascular abnormalities, which do not necessarily coexist. Others applied the term aberrant vessels to

periportal vessels only[31,32]. Again, others called this lesion "herniated PV"[26] or simply considered it a component of "hepatoportal sclerosis" without using a specific terminology.

other commonly used term is "shunt vessels".[9,19,33,34] However, some authors used "shunt sels" to refer to periportal abnormal vasculature[34]. Furthermore, it is not clear whether se abnormal vessels were really shunts. In the study by Ohbu et al.[30], using serial paraffin sections, these vessels were seen opening into sinusoids, indicating they were not intrahepatic shunts connected to the terminal hepatic veins, but that they presumably represented dilated inlet venules. Indeed, these vascular structures have a thin wall similar to the inlet venules. Waiting for a better understanding of the pathogenic events that lead to this change, we suggest keeping the most descriptive term among those available, that is "*herniated PV*". This term immediately reflects the impression we have looking at the biopsy. We strongly recommend abandoning all the other terminologies.

Recommended term: herniated PV

Definition: A portal vein from the portal tract directly abutting periportal parenchyma (Fig. 2 and Table 1).

Increase in the number of portal vascular spaces

An increased number of thin walled vascular spaces in PTs, often without an effective portal vein, is a well-recognized morphologic feature of INCPH, first described by Mikkelsen et al. 1965[6]. This finding has also been included in the description of hepatoportal sclerosis[10]. yak et al.[7] considered them as obliterative change of smaller branches and defined them as "few small capillary-like venous channels dispersed in the fibrosed portal tracts". However, size of these vessels was variable. Krasinksas et al.[16] referred to such alteration as "fragmentation" of portal vein radicles and included it under the umbrella of aberrant vessels. her terms used in the literature included "PT angiomatosis", "angiomatoid lesion"[23] and

"angiomatous transformation of the PT"[35]. It is very unlikely that such an anomaly reflects neoplastic or malformed vascular proliferation, as the terminology might suggest; its pathogenesis remains unknown. We suggest discontinuing the use of these different names and replace them with the descriptive, non-committal term, "*hyper-vascularized portal tract*", which simply means that there are more vascular structure than expected in a normal PT.
Recommended term: hyper-vascularized portal tract.
Definition: multiple thin walled vascular spaces in PT (Fig. 3 and Table 1).

Periportal vessels

Periportal changes in INCPH consist of abnormal vascular spaces immediately adjacent to a tal tract, which may or may not contain a normal PV[11,13,19,26,30]. Periportal abnormal vascular spaces may be single or multiple with lumen of different sizes. Similar changes have been also found in cases of extrahepatic portal vein obstruction and nodular regenerative hyperplasia, both entities known to be associated with non-cirrhotic portal hypertension. The gin of these vascular spaces is also not clear. Fukuda et al.[36] provided evidence that they were portal in nature, on autopsy and biopsy materials of idiopathic PH, and in experimental animal models. The various terms used to refer to this abnormality include aberrant sels[16,29,30], cavernous transformation[26], paraportal shunting vessels[7] and gasinusoids[37,38]. As already observed, "aberrant vessels" has been used as an umbrella term also including intra portal vessel changes. Both angiomatoid malformation and cavernous transformation are ambiguous terms. In the common medical language, malformation means deviation from normal morphology usually on a genetic/congenital base. Cavernous transformation of the portal vein currently indicates a rare condition consisting of portosystemic or porto-portal collaterals that develop as long-term sequelae of portal vein thrombosis. We also discourage the use of the terms "paraportal shunting vessels" and

"megasinusoids" since neither the shunt function nor the sinusoidal origin are proven. In addition, the term megasinusoid has been used to describe sinusoidal ectasia, which is a common accompanying change in cases of INCPH.

To avoid confusion about the unclear origin of this vascular abnormality, we again recommend using a purely descriptive term and suggest to name this finding "*periportal normal vessels*"

Recommended term: periportal abnormal vessels.

Definition: single or multiple thin-walled vascular spaces of different caliber outside, but in close contact with the portal tract (Fig. 4 and Table 1).

Conclusion

Aiming at simplification and providing a basis for standardization, the nomenclature proposed herein is intended to be descriptive enough so that it can be used without pathophysiological implications. Our knowledge of the causes and morphogenesis of vascular al erations and of natural history in INCPH is still unsatisfactory. The use of consistent nomenclature and definitions in both clinical and research setting will facilitate future investigations and standardization of diagnostic criteria.

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Maria Guido prepared the manuscript draft.

All the Authors revised the manuscript and approved the final version

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Table 1: summary of proposed nomenclature and definition of portal/periportal INCPH lesions.

posed term	Definition	Terms to be discarded
Portal vein stenosis	Incomplete (Fig. 1A) or complete (Fig. 1B) obliteration of portal vein branches ± thickening of the wall	Phlebosclerosis; obliterative portal venopathy; portal vein obliteration; hepato-portal sclerosis
Herniated portal vein	A portal vein from the portal tract directly abutting periportal parenchyma (Fig. 2A-B)	Aberrant vessels; hepatoportal sclerosis; shunt vessels
Hyper-vascularized portal tract	Multiple thin walled vascular spaces in PT (Fig 3A-B)	Fragmentation of portal vein radicles; portal tract angiomatosis; angiomatoid lesion; angiomatous transformation of portal tract
Periportal abnormal vessels	Single or multiple thin-walled vascular spaces of different caliber outside, but in close contact with the portal tract (Fig. 4A-B)	Aberrant vessels; cavernous transformation; paraportal shunting vessels; megasinusoids

Figure legends

Fig. 1: Sclerotic portal tracts with partial (A) and complete (B) stenosis of the portal vein branch. (H&E; 20X and 60x).

. 2A and 2B): Examples of herniated portal veins (H&E; 20x and 40x)

. 3A and 3B: Hyper-vascularized portal tract is characterized by the presence of multiple vascular profile with thin wall and lumen of different caliber. In panel B an abnormal periportal vessel (arrowhead) is also visible (H&E; 20x).

Fig. 4: Abnormal periportal vessels (*) have thin walls and small (A,B) or large (B) caliber. In both cases, a normal portal vein branch is no visible (H&E; 20x and 40x).