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Different cytokeratin and neuronal cell adhesion molecule staining patterns in focal nodular hyperplasia and hepatic adenoma and their significance

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Summary

Differentiating focal nodular hyperplasia from hepatic adenoma can be challenging. Cytokeratin 7, neuronal cell adhesion molecule, and cytokeratin 19 are differentially expressed in hepatocytes, biliary epithelium, and possibly hepatic progenitor/stem cells. CD34 is known to have altered expression patterns in the hepatic endothelium in conditions associated with abnormal perfusion and in hepatocellular carcinoma. The purpose of this study was to examine the expression pattern of these markers in focal nodular hyperplasia and hepatic adenoma and assess their diagnostic use. Ten resection specimens each of hepatic adenoma and focal nodular hyperplasia (including a case of telangiectatic focal nodular hyperplasia) were selected for the study. Immunohistochemical analysis was performed using antibodies against cytokeratin 7, cytokeratin 19, neuronal cell adhesion molecule, and CD34 on formalin-fixed, paraffin-embedded sections from each case. The staining patterns and intensity for each marker were analyzed. In hepatic adenoma, the cytokeratin 7 stain revealed strong positivity in hepatocytes in patches, with a gradual decrease in the staining intensity as the cells differentiated towards mature hepatocytes. Although bile ducts were typically absent in hepatic adenoma, occasional ductules could be identified with cytokeratin 7 stain. In focal nodular hyperplasia, cytokeratin 7 showed strong staining of the biliary epithelium within the fibrous septa and staining of the peripheral hepatocytes of most lobules that was focal and weaker than hepatic adenoma. Cytokeratin 19 and neuronal cell adhesion molecule showed patchy and moderate staining in the biliary epithelium of the ductules in focal nodular hyperplasia. While in the hepatic adenoma, cytokeratin 19 showed only rare positivity in occasional cells within ductules, and neuronal cell adhesion molecule marked occasional isolated cells in the lesion. CD34 showed staining of sinusoids in the inflow areas (periportal areas) in both focal nodular hyperplasia and hepatic adenoma. One case of telangiectatic focal nodular hyperplasia revealed both hepatic adenoma–like and focal nodular hyperplasia–like staining patterns. Distinct cytokeratin 7, cytokeratin 19, and neuronal cell adhesion molecule staining patterns are seen in hepatic adenoma and focal nodular hyperplasia possibly suggest activation of different subsets of hepatic progenitor/stem cell and can be diagnostically useful.

Keywords

Hepatic adenoma; Focal nodular hyperplasia; Immunohistochemistry

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1. Introduction

Well-differentiated hepatocellular lesions that include hepatic adenoma (HA) and focal nodular hyperplasia (FNH), can be difficult to differentiate on needle biopsies and can pose diagnostic dilemmas in clinical practice. Although HA is a benign neoplasm with a risk of spontaneous bleeding, rupture, and malignant transformation, FNH is a hyperplastic lesion that has a stable course with no significant complications. Therefore, HA is often treated surgically, whereas FNH is usually managed conservatively [1]. Given the important difference in treatment modality, the correct diagnosis of hepatic mass lesions is pivotal. The diagnosis of these lesions is largely dependent on histologic features. Special stains including immunohistochemical analysis are seldom used in this setting. It is well recognized that diagnostic difficulties arise in needle biopsies because of sampling issues and overlapping histologic features that could lead to inappropriate management of the underlying lesion.

Immunohistochemical stain for cytokeratin (CK) 7 has been used in practice to identify bile ducts and proliferating ductules in liver biopsies from mass lesions to differentiate normal from lesional tissue, as well as HA from FNH [2,3]. However, we have often noted distinct staining patterns for CK7 in these lesions that have not been hitherto emphasized in the literature. The goal of this study was to evaluate the staining patterns and diagnostic use of CK7, CK19, and neuronal cell adhesion molecule (NCAM) in HA and FNH. These markers are known to differentially stain hepatocytes, biliary epithelium and possibly the hepatic progenitor cells (HPCs)/stem cells [4–6]. CD34, a marker of vascular endothelium, has been shown to be useful in differentiating well differentiated hepatocellular carcinoma (HCC) from benign hepatic parenchyma and, occasionally, from HA [7–10]. We therefore wanted to investigate whether CD34 had any diagnostic use in differentiating HA from FNH.

2. Materials and methods

The pathology archives were searched from 1990 to 2007 for resection specimens with the diagnosis of either HA or FNH. Ten cases each of HA and FNH, including telangiectatic FNH (n = 1), were selected for the study. The diagnoses in all the cases were made on histologic examination of routinely processed tissue. The hematoxylin and eosin–stained sections in all cases were reviewed, and the diagnoses were confirmed applying standard diagnostic criteria [1].

Immunohistochemical analysis using the indirect immunoperoxidase method was performed using antibodies against CK7 (Dako Cytomation, Carpinteria, CA; dilution, 1:200), CK19 (BioGenex, Rocklin, CA; dilution, 1:1), NCAM (CD56) (Vector Laboratories, Burlingame, CA; dilution, 1:100), and CD34 (BioGenex, San Ramon, CA; dilution, 1:4) on 4-μm-thick, formalin-fixed, and paraffin-embedded representative sections from each case. Appropriate positive and negative controls were used. Sections of normal liver present in each case served as internal control for CK7, CK19, and NCAM, and the venular endothelium served as internal control for CD34 in each case. The staining patterns and intensity for each marker were analyzed and recorded. The intensity of staining was subjectively graded as negative, weak, moderate, and strong. Two-tailed Fisher exact test was used for statistical analysis, and $P < .05$ was considered significant.

3. Results

Different intensities and patterns of staining were noted with these markers in the normal, HA, and FNH. The staining patterns are summarized in Table 1.

3.1. Normal liver

The biliary epithelium was strongly and diffusely positive for CK7, which acted as internal control (Fig. 1A). Mild and focal staining was seen in the periportal hepatocytes of normal liver in only 1 case. CK19 revealed weak to moderate patchy staining of biliary epithelium (Fig. 1B) in all cases, with no staining of the hepatocytes. NCAM showed negative to weak staining of the biliary epithelium in all cases. In addition, the activated hepatic stellate cells, which were present in liver tissue adjacent to the lesion (HA or FNH) in 6 cases also showed intense staining (Fig. 1C). CD34 was expressed in the endothelium of the central vein, portal vein, and a few sinusoids in the inflow area (inflow pattern) in an occasional lobule. The centrilobular sinusoids were consistently negative (Fig. 1D).

3.2. Hepatic adenoma

There was patchy moderate to strong CK7 staining of hepatocytes (Fig. 2A). The positively stained cells were found scattered singly or in aggregates of varying density. CK7 staining showed gradual decrease in intensity as the cells differentiated toward mature hepatocytes (Fig. 2B). The hepatic cells with strongest positivity for CK7 were often small with ovoid nucleus and scant cytoplasm, whereas cells with moderate intensity of staining were intermediate-sized polygonal cells, and cells with weakest staining for CK7 were larger and similar to mature hepatocytes. Although bile ducts were typically absent in HA, occasional ductules could be identified with CK7 stain (Fig. 2B). CK19 did not stain or only weakly stained a rare bile ductule in the lesion (Fig. 2C). There was no staining for CK19 seen in the hepatocytes. NCAM revealed strong staining in a rare epithelial cell of bile ductules or rare isolated single cell in the lobules (Fig. 2D). CD34 showed positive sinusoidal staining in the periportal area (inflow pattern) in 7 of 10 cases. The remaining 3 cases (n = 3/10), in addition, had areas of diffuse staining (Fig. 2E).

3.3. Focal nodular hyperplasia

There was strong CK7 staining of the biliary epithelium within the fibrous septa. The CK7 staining in the hepatocytes was milder and focal compared with HA and was seen at the periphery of most lobules with no centrilobular staining (Fig. 3A, B). With CK19, there was weak to moderate patchy staining of biliary epithelium of bile ductules (Fig. 3C); no staining was seen in the hepatocytes. With NCAM, strong membranous staining of the biliary epithelium was seen (Fig. 3D) without any staining in the hepatocytes. In addition, no isolated single cells in the lobule were marked by NCAM unlike, in an HA. CD34 showed strong and diffuse staining of the periportal sinusoids (inflow pattern) (Fig. 3E). CD34 did not stain the centrilobular sinusoids. However, occasional small hepatocytic nodules that mimic cirrhotic nodules showed diffuse staining of the entire nodule.

The case of telangiectatic FNH had characteristic features such as lack of central scar, presence of dilated sinusoids, and expansile areas of regenerating hepatocytes containing small vessels, adjacent to areas with more typical ductular proliferation. CK7 and CD34 showed both HA-like and FNH-like patterns in different areas of the lesion (Fig. 4A, B). CK19 and NCAM showed no staining in the HA-like areas, whereas the FNH-like areas revealed positive staining of the bile ducts and ductules.

Based on these observations, the patterns in each case for each marker were categorized as FNH- or HA-like (Table 2). FNH-like staining pattern included strong CK7 staining in the bile ducts and ductules with weak to moderate staining of few hepatocytes in close proximity to biliary epithelium at the periphery of the lobule, weak to moderate patchy CK19 staining of the biliary epithelium, strong and membranous NCAM staining of the biliary epithelium, and strong CD34 staining of the periportal sinusoids (inflow pattern). A typical HA-like pattern included patchy moderate to strong CK7 staining of the hepatocytes,

with decreasing staining intensity of the CK7 as the cells differentiated from small cells towards mature hepatocytes; weak CK19 staining in an occasional bile ductule in the lesion; strong and patchy NCAM staining of bile ductules or isolated single cells; and either inflow pattern or diffuse staining of the sinusoidal endothelium with CD34. Statistical analysis revealed that CK19 and NCAM were most useful in differentiating FNH and HA ($P < .001$). Staining with CK7, although useful, did not reach statistical significance ($P < .069$), whereas combining all the 3 antibodies produced the best results ($P < .0001$).

4. Discussion

A common dilemma when dealing with hepatocytic mass lesions of the liver is differentiation between an HA and FNH. A confident diagnosis can often be made based upon imaging characteristics and clinical history. However, the diagnosis may remain uncertain even after multiple imaging modalities, warranting a liver biopsy. Distinction between HA and FNH on a liver biopsy specimen in routine practice can be very challenging and is frequently resolved only in resection specimens.

FNH is generally accepted to be a hyperplastic response to hyperperfusion by the anomalous arteries found in the central stellate scar of the lesion. Multiple branches from the anomalous large artery radiate through the fibrous septa to the periphery. These branches divide the masses into multiple small nodules or cords of normal appearing hepatocytes. The scar-like tissues within FNH nodules are composed of abnormally large portal tracts including large feeding arteries, branches of portal veins, and bile ducts. Hepatic adenomas are hepatocytic neoplasms characterized by the absence of true portal tracts. The cells are arranged in normal or thickened trabeculae interspersed with prominent unpaired arteries and thin walled blood vessels or sinusoids. True portal tracts and bile ducts are absent, thereby differentiating HA from FNH [1].

In our study, CK7 identified 3 distinct population of hepatocytic cells, namely, the dark-staining “small cells” (HPCs/stem cells), the moderate-staining “intermediate hepatocytes,” and large mature hepatocytes, in both HA and FNH, as has been previously reported [2,3]. Areas of CK7 stained hepatocytic cells were more prominent and extensive in HA compared to FNH. CK7 staining produced distinct patterns in HA and FNH in 15 (75%) of 20 cases, with overlap in 5 cases including 1 case of telangiectatic FNH. Because of this overlap, CK7 staining pattern alone cannot be used as a definitive distinguishing feature between these 2 lesions.

CK19 and NCAM showed reliable differentiating patterns in all cases. CK19 showed weak to moderate patchy staining of biliary epithelium in FNH, whereas it was negative or showed only weak staining in a rare bile ductule in HA. CK19 did not stain the hepatocytes in either lesion. NCAM revealed strong staining in rare biliary epithelial cells of a ductule or isolated single cells in HA. Although, in FNH, no isolated single cells in the lobules were marked by NCAM, it stained the biliary epithelium. Although the staining patterns for CK19 and NCAM were distinctive in HA and FNH with little overlap, the diagnostic areas can be patchy and staining can be weak, resulting in diagnostic issues on needle biopsies.

In the case of telangiectatic FNH, all markers showed both HA-like and FNH-like areas, which corresponded to different histologic patterns in the lesion. This finding is in agreement with the current concept that telangiectatic FNH should be considered as a variant of HA [11,12].

CD34 is an endothelial surface adhesion molecule, which is normally present in portal and central veins of the liver but is absent in the sinusoids of the liver [13]. However, under different conditions of vascular perfusion, the sinusoidal endothelium undergoes phenotypic

alterations and helps to differentiate the inflow (periportal) from the outflow (centrilobular) areas [14]. In addition, CD34 shows diffuse sinusoidal staining in HCC because of "capillarization" of the sinusoids, which has been found to be diagnostically useful [7–10]. A single comparative study looking at CD34 staining pattern in FNH and HA in cytology specimens has been previously reported [8]. However, to our knowledge, this is the first comparative study of the same in liver resection specimens. In our study, CD34 showed staining of the sinusoids in the inflow area (inflow pattern) in most cases (14/20 cases). Some of the small nodules in the FNH and few HAs showed diffuse staining of the sinusoidal endothelium. This possibly also represents an inflow pattern that appeared diffuse because of a tangential sectioning of a larger nodule or represents an exaggerated inflow pattern in small nodules.

Overall, CD34 staining pattern did not show any reliable differentiating features in FNH and HA. This is in agreement with the previously reported study on FNA specimens [8]. However, CD34 stain could be potentially useful in differentiating HA from HCC, as the inflow pattern is preserved in many HAs in contrast to the diffuse staining of sinusoidal endothelium in HCC. However, diffuse staining does not exclude the possibility of HA, as 3 cases (n = 3/10) in our study showed areas of diffuse CD34 staining. This finding needs further validation.

The pattern of staining for CK7, CK19, and NCAM in these lesions raises many interesting questions regarding the role of HPCs in their pathogenesis. The existence of HPCs and their ability to differentiate towards hepatocyte and biliary lineage has been well recognized [6,15,16]. They are thought to reside in the terminal ductules (canal of Herring) and are responsible for regeneration in the event of severe liver injury [17,18]. Their phenotype and the gene expression profile have also been described recently [4–6]. These cells express markers such as CK7, CK19, NCAM, OV6 (a marker for oval cells and the terminally differentiated bile ducts), HepPar1, albumin, α-1 antitrypsin, and occasionally α-fetoprotein. NCAM, in addition, is also known to be expressed in activated hepatic stellate cells and myofibroblasts, but not in mature hepatocytes [4,5,19]. The differential staining of CK7, CK19, and NCAM in HA and FNH suggest that different subsets of HPCs are involved in the histogenesis of these lesions. The role of HPCs/stem cell population in the genesis of hepatocytic lesions has been explored in some isolated studies [2,6]. Libbrecht et al [2] have shown that HPCs are present in a considerable proportion of HAs (5/10 cases) using CK7, CK19, OV-6, and chromogranin-A. Roskams et al [6] have shown that HPCs are present in FNHs using CK7, CK8, CK18, CK19, chromogranin A, OV-6, and NCAM. They suggested that the ductular reaction in FNH at least partly resulted from activation of HPCs. Our study shows that HPCs are activated in all cases of HA and FNH, and possibly, different subsets of HPCs are involved in each lesion. In HA, hepatocytic growth appears to occur from HPC that are committed toward hepatocytes. They may reside within the lesional hepatocytes or in the rare ductules identified with the help of CK7 and CK19 stains. These ductules are not easily apparent on H&E stain, and their presence in HA has only rarely been highlighted in standard texts and literature [1,2]. One should be aware of these findings, especially when reviewing immunostains for CK7 and CK19 to avoid potential diagnostic errors. In contrast, in FNH, there is a proliferation of both hepatocytes and bile ductules, suggesting that a more primitive cell capable of differentiating toward both hepatic and biliary lineage is likely to be involved. In HAs, CK7 identified a higher density of isolated small (dark-staining) cells than NCAM. Although we did not look at coexpression of markers in this study, based on the location of the cells, we suspect that NCAM is identifying a subset of the "small cells" marked by CK7 rather than a totally different subset of HPCs, and these are committed toward hepatic lineage. In addition, that the NCAM and CK19 do not stain the CK7 positive "intermediate hepatocytes" raises the possibility that NCAM and CK19 are a marker of probably more primitive HPCs than those marked by only

CK7 or identify a subset of HPC committed towards biliary lineage. These findings are in concordance with the recently proposed differentiation scheme of stem cells towards hepatocytic and biliary lineages [5].

In conclusion, we have shown that CK7, CK19, and NCAM show distinct staining patterns in normal liver, FNH, and HA. The differences in staining patterns are likely due to activation of different subsets of HPCs, and the study provides support for different phenotypes of committed hepatic progenitor cells. In HA, the activation is unidirectional (only hepatocytic), whereas in FNH, the activation is bidirectional (both biliary and hepatocytic). Although diagnosis of these lesions is seldom problematic in resection specimens, difficulties may be encountered in biopsies where these markers may be useful. Some overlap exists in the staining pattern and a combination of stains including CK7, CK19, and/or NCAM rather than a single stain could be helpful in diagnostically challenging cases. However, further prospective studies on needle biopsies and diagnostically difficult cases are needed to validate these findings.

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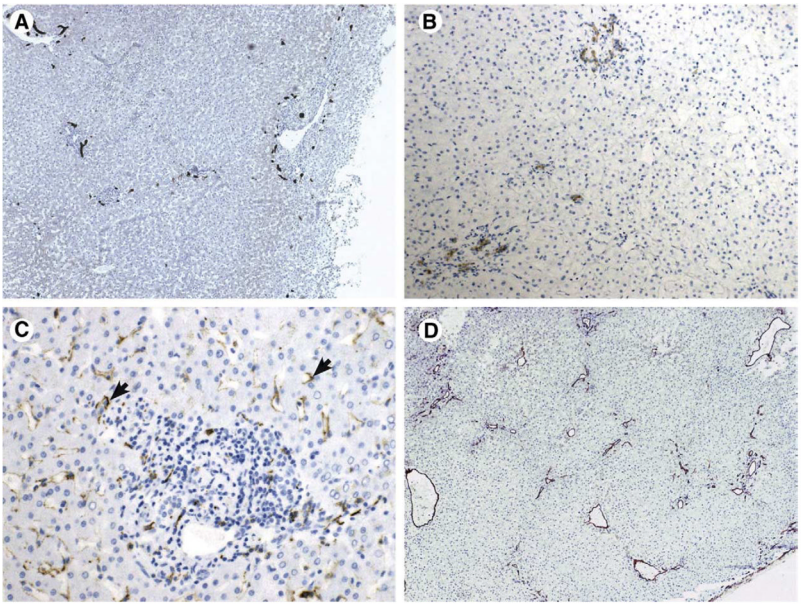

Fig. 1.

Normal liver. A, Strong expression of CK7 in the bile ducts and ductules. B, Weak to moderate patchy CK19 staining of biliary epithelium. C, Weak NCAM staining of the biliary epithelium and hepatic stellate cells (arrows). D, Strong staining of CD34 in central vein, portal vein and few sinusoids in the inflow area. (Magnification: A × 40, B × 100, C × 200, D × 40.)

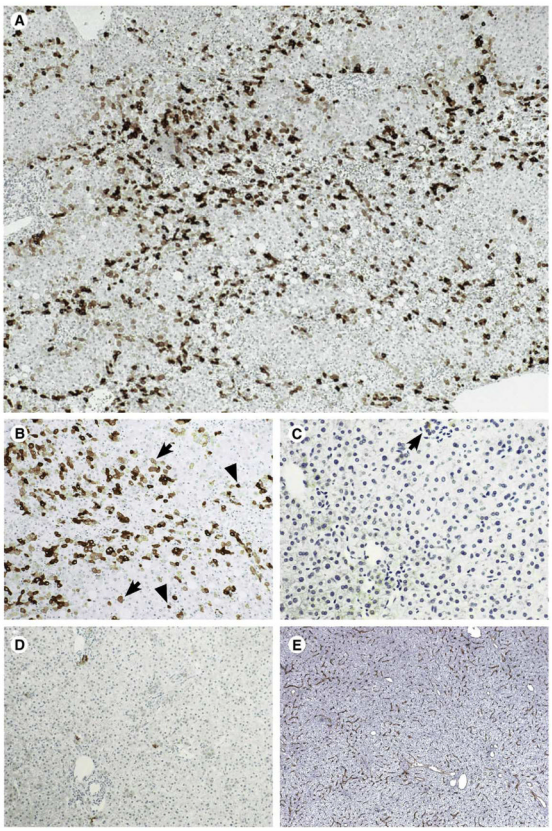

Fig. 2.

Hepatic adenoma. A, Patchy moderate to strong CK7 staining of the hepatocytes. B, Decreasing staining intensity of the CK7 as the cells differentiate from stem cells (arrow heads) toward intermediate hepatocytes (arrows). C, Weak CK19 staining in an occasional the bile ductule (arrow) in the lesion. D, Strong and patchy NCAM staining of bile ductules, isolated single cells, and scattered stellate cells. E, CD34 showing a mixed pattern of staining (inflow and diffuse). (Magnification: A × 40, B & C × 200, D × 100, E × 40.)

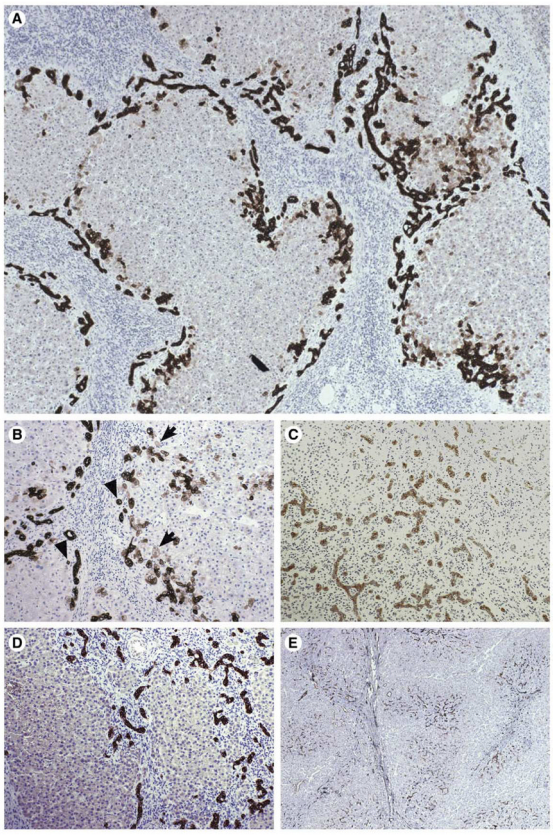

Fig. 3.

Focal nodular hyperplasia. A, Strong CK7 staining in the bile ducts and ductules with focal staining in the peripheral hepatocytes of a lobule. B, Weak to moderate staining of intermediate hepatocytes (arrows) in close proximity to biliary epithelium (arrowheads) at the peripheral of the lobule. C, Weak to moderate patchy CK19 staining of the biliary epithelium. D, Strong, membranous NCAM staining of the biliary epithelium. E, Strong and diffuse CD34 staining of the periportal sinusoids (inflow pattern). (Magnification: A × 40, B–D × 200, E × 40.)

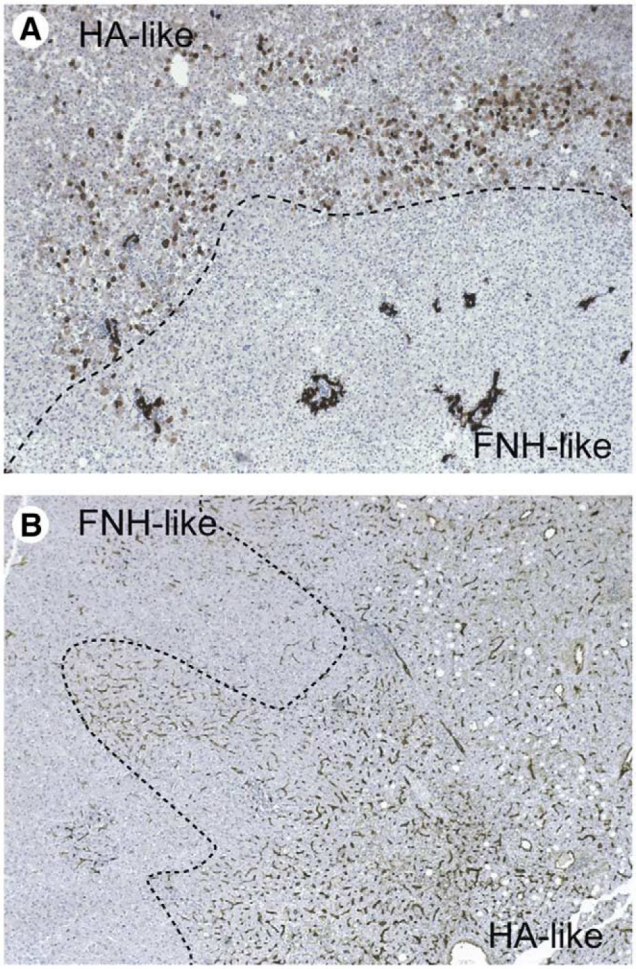

Fig. 4.

Telangiectatic FNH. A, CK7 showing mixed FNH- and HA-like staining pattern. B, CD34 showing the inflow pattern in the FNH component, and diffuse pattern in the adenomatous component. (Magnification: A & B × 100.)

Table 1

Summary of staining patterns for each antibody

	Normal	FNH	HA
CK7	Biliary epithelium and rare isolated hepatocytes	Biliary epithelium and focal staining in peripheral hepatocytes	Intense staining in hepatocytes and rare ductules
CK19	Weak to moderate staining of biliary epithelium.	Weak to moderate staining of biliary epithelium.	Negative or weak staining of rare bile ductules in the lesion.
NCAM	Negative to weak staining of the biliary epithelium; no staining of hepatocytes.	Strong membranous staining of the biliary epithelium; no staining of hepatocytes.	Strong staining only in rare biliary epithelial cell or isolated single cells amidst hepatocytes in the lesion
CD34	Rare sinusoids in the inflow area	Sinusoids in the inflow areas only	Sinusoids in inflow areas in most cases. Some cases with focal diffuse staining

Table 2

Number of cases with typical pattern for each antibody

	HA (n = 10)			FNH (n = 10)		
	CK7	**CK19**	**NCAM**	**CK7**	**CK19**	**NCAM**
HA-like	8	10	10	3	0	0
FNH-like	2	0	0	7	10	10