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Cytological-pathologic Correlation

Interpretation of core biopsy of liver mass lesions: A comparison study between cytopathologist and gastrointestinal pathologist☆,☆☆

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ABSTRACT

Context: Core biopsy (CB) is a main tool for diagnosis of liver mass lesions. When CB is performed with fine needle aspiration (FNA), the CB may be interpreted by a cytopathologist or gastrointestinal pathologist.
Objective: This study compares interpretation of liver mass biopsy between cytopathologist and gastrointestinal pathologist in the era of subspecialty practice.
Design: 349 liver mass lesions with FNA and CB performed during a 5-year period were retrieved. All cases were initially interpreted by a cytopathologist and retrospectively reviewed by a gastrointestinal pathologist.
Results: The overall agreement was 95.1% (332/349 cases). There was agreement on 57/65 non-neoplastic cases (87.7%) with 8 (12.3%) discordant cases including 4 steatosis (steatohepatitis missed in 3 cases, 1 re-interpreted as focal nodular hyperplasia [FNH]); 3 inflammation (1 necrotizing granulomatous inflammation, 1 massive necrosis instead of fibrosing cholestatic hepatitis, and 1 hepatocellular carcinoma [HCC] was missed); and 1 initially deemed normal re-interpreted as FNH. There was agreement on 275/284 neoplastic cases (96.8%), with 9 (3.2%) discordant cases including: 2 initially interpreted as HCC (1 metastatic adrenal cortical carcinoma, 1 cholangiocarcinoma); 3 adenocarcinomas (2 further defined as prostatic primary, 1 well-differentiated neuroendocrine tumor [WDNET]); 2 metastatic carcinomas (1 tumor-induced fibrosis instead of cirrhosis, 1 LCNEC re-interpreted as WDNET); 1 poorly differentiated carcinoma (re-interpreted as LCNEC); and 1 sarcomatoid carcinoma (re-interpreted as leiomyosarcoma).
Conclusion: Cytopathologist and gastrointestinal pathologist are highly concordant in the interpretation of neoplastic liver mass CB. Consultation may improve accuracy in certain non-neoplastic biopsies and neuroendocrine neoplasms.

1. Introduction

Traditionally pathology practice in the United States is general practice, in which the pathologist covers all aspects of pathology services including both anatomic and clinical pathology. This practice model is largely maintained in most small private pathology laboratories. A survey has found that the vast majority of academic medical centers have adopted at least a partial subspecialty practice model, in which the pathologist focuses his/her practice to one or several subspecialties [1]. The perceived benefits of subspecialty service include: dedicated expert pathologists for resident teaching, more consistent pathology reporting, and reduced diagnostic discrepancy, which results in overall improved quality of care and clinician satisfaction [1,2].

The liver is a common site for metastatic malignancies but may also be involved by benign or malignant primary neoplasms. Fine needle aspiration (FNA) and core biopsy are essential diagnostic procedures for patients with focal liver mass lesions. FNA cytology alone has not been shown to be an accurate method in the diagnosis of diffuse liver diseases such as cirrhosis or hepatitis, but can be helpful to exclude neoplasms when non-neoplastic liver disease simulates mass lesions on imaging studies. One commonly employed diagnostic protocol includes radiologist performed FNA with rapid onsite adequacy evaluation (ROSE) by cytopathologist followed by acquisition of core needle biopsy specimen.

When a core biopsy is performed along with fine needle aspiration (FNA), the core biopsy may be interpreted by the same cytopathologist

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who reviews the FNA smear or separately by a gastrointestinal pathologist, depending on the practice in each institution. Our institution follows the former model. It is unknown which practice model is better for patient care, and this topic is seldom studied. This study was designed to compare the interpretation of liver mass core biopsy between cytopathologist and gastrointestinal pathologist in the era of subspecialty practice.

2. Materials and methods

2.1. Case selection

After institutional review board approval, a CoPath database search for cases of liver mass lesions with a concurrently performed FNA and core biopsy during a 5-year period (2010–2015) was performed. All cases were initially interpreted by one of the pathology department's four board-certified cytopathologists, none of whom are also GI pathology specialists. Repeat biopsies and biopsies which had previously received GI pathologist consultation/review were excluded.

2.2. Case analysis and categorization

All available slides were retrospectively reviewed by a gastrointestinal pathologist (ZY) and blinded from the original diagnosis. Additional stains were performed as indicated. The original cytopathology diagnoses were classified as non-neoplastic or neoplastic. After comparing these reports with the GI pathologist's interpretations, the discordant cases were designated as a major or minor discrepancy. A major discrepancy is one that could have resulted in altered patient management. Examples of major discrepancies include metastatic lesions originally interpreted as hepatocellular neoplasm, or carcinoma interpreted as benign reactive/ inflammatory lesion. A minor discrepancy is defined as one that would be unlikely to influence patient management. Examples of minor discrepancy include: degree of steatosis, or further delineation of an inflammatory process in a cirrhotic liver.

3. Results

3.1. Overall clinical and pathologic characteristics

Four hundred and twenty-eight cases of liver mass lesions with concurrent FNA and core biopsy were initially identified during the five year period. After excluding repeat biopsies, cases also reviewed by a GI pathologist prior to sign-out, and cases for which the slides were unavailable, three hundred and forty-nine cases were included in the study. The mean age of the patients was 63.4 years, with a male to female ratio of 1.3 to 1. Two hundred and twenty-nine patients (65.6%) had a clinical history of malignant neoplasm, mostly were adenocarcinomas of the GI organs (106 cases, 30.4% of total cases). Twenty-two patients (6.3%) had cirrhosis (Table 1).

Among the 349 cases within the cohort, cytopathologist-rendered preliminary rapid on-site evaluation diagnosis (ROSE) was performed in 347 cases. The overall concordance rate of ROSE, final FNA smear diagnosis, and core biopsy diagnosis was 91.9% with 28 total discrepancies. ROSE was performed in 64 of 65 non-neoplastic cases, as reported by the cytopathologist on core biopsy; there was 100% concordance between ROSE and final FNA smear diagnoses. Nine cases (14.1%) showed a discrepancy between ROSE and core biopsy diagnosis. In 7 cases the ROSE diagnosis was “positive for malignant cells” or “atypical cells” where the core biopsy was diagnosed as “benign liver, negative for tumor.” In one case the ROSE was read as “suspicious” and the core biopsy was “non-diagnostic.” For another case, the ROSE diagnosis was “lesional tissue present” and the core biopsy diagnosis was “benign hepatic tissue.”

ROSE was performed in 283 of the 284 cases for which the core biopsies were interpreted as neoplastic by the cytopathologist; only 2 cases (0.7%) showed a discrepancy between ROSE and final FNA smear diagnoses. The ROSE diagnoses were “adequate, favor hepatocellular lesion” and “hepatocytes present”, respectively, and both were “consistent with metastatic adenocarcinoma” on final FNA smear report. Eighteen cases (6.4%) showed a discrepancy between ROSE and core biopsy diagnosis. Three cases showed “blood only” on ROSE and the core biopsies showed “metastatic adenocarcinoma”, “metastatic gastrointestinal stromal tumor”, and “cavernous hemangioma,” respectively. In 12 cases the ROSE was diagnosed as benign hepatic cells, but the core biopsy showed metastatic lung, pancreas, breast, or neuroendocrine neoplasms. In 2 cases the ROSE diagnoses were “positive for malignant cells” and the core biopsy diagnoses were “rare atypical cells.” In one case the ROSE was reported as “atypical lymphoid cells” while the core biopsy was reported as “high grade neuroendocrine carcinoma”.

Sixty-five of 349 cases (18.6%) were initially diagnosed as non-neoplastic disease on core biopsy: 54 (15.5%) were concordant between core biopsy and smear, and 11 (3.2%) were reported as neoplastic on smear only. Upon retrospective review, the gastrointestinal pathologist agreed on 57 of the 65 non-neoplastic core biopsy diagnoses (87.7%), and disagreed on 8 cases (12.3%) (Table 2). Two hundred and eight-four of 349 cases (81.4%) were initially diagnosed as neoplastic lesions on core biopsy: 259 (74.2%) were concordant between core biopsy and smear, and 25 cases (7.2%) were reported as negative for tumor on smear. The gastrointestinal pathologist agreed with the core biopsy diagnoses on 275 of 284 (96.8%) neoplastic cases and disagreed on 9 cases (3.2%) (Table 3). Thus there was significantly more discordant cases in non-neoplastic diagnoses (Fisher's exact test, $p = 0.006$). The discrepant diagnoses were essentially equally distributed among the group of four cytopathologists in the department's cytopathology unit.

Table 1
Clinicopathologic features of the 349 patients with concurrently performed fine needle aspiration biopsy and core biopsy for liver mass lesions from 2010 to 2015 at Penn State Hershey Medical center.

Feature		Number or value	Percentage (%) of total
Age (yrs.)	Mean	63.4	–
	Range	20–97	
Gender	Female	154	44.1
	Male	195	55.8
Cancer history	Pancreatobiliary	61	17.4
	Colorectal	31	8.8
	Breast	26	7.4
	Genitourinary	22	6.3
	Lung	18	5.1
	Non-colorectal GI	14	4.0
	Melanoma	13	3.7
	Prostate	10	2.8
	Hematologic	8	2.2
	Hepatocellular CA	7	2.0
	Neuroendocrine	7	2.0
	Mesenchymal	5	1.4
	Head/neck	4	1.1
	Other	3	0.8
Cirrhosis		22	6.3
Liver transplant		1	0.2

3.2. Non-neoplastic diagnoses

The initial non-neoplastic diagnoses were as follows: inflammatory/ hepatitis (22), no pathologic alteration (19), cirrhosis (12), steatosis (9), benign cyst (2), and mucin (1). Of the 22 biopsies initially diagnosed as an inflammatory condition, 3 cases (13.6%) showed discrepant diagnoses including: 1 re-interpreted as necrotizing granulomatous inflammation, 1 showed massive necrosis instead of fibrosing cholestatic hepatitis with marked fibrosis (Fig. 1), and 1 case revealed scant viable

Table 2
Summary of non-neoplastic diagnoses and revised diagnoses by GI pathologist.

Cytopathologist diagnosis	Total cases (%)	Discordant cases (%)	GI pathologist diagnosis
Inflammatory disease	22 (33.8)	3 (4.6)	• Necrotizing granuloma, instead of steatohepatitis, lipogranuloma • Necrotic HCC, instead of infarction • Massive necrosis, instead of FCH with fibrosis
NPA	19 (29.2)	1 (1.5)	• FNH
Cirrhosis	12 (18.4)	0 (0)	
Steatosis	9 (13.8)	4 (6.1)	• 3 Steatohepatitis, instead of steatosis • FNH/HCA, instead of steatosis
Cyst	2 (3.1)	0 (0)	
Other	1 (1.5)	0 (0)	
Total	65 (100)	8 (12.3)	–

%: percentage of total non-neoplastic cases; FCH: fibrosing cholestatic hepatitis; NPA: no pathologic alteration; FNH: focal nodular hyperplasia; HCA: hepatocellular adenoma.

hepatocellular carcinoma (HCC) which was initially thought necrosis (Fig. 2). Of the 9 cases with an initial diagnosis of steatosis, four cases showed discrepant diagnoses (44.4%) (steatohepatitis was not mentioned in 3 cases) (Fig. 1) and one case was re-interpreted as focal nodular hyperplasia vs hepatocellular adenoma. Lastly, 1 case initially deemed normal was re-interpreted as focal nodular hyperplasia. Diagnoses were concordant in all 12 cases of cirrhosis and 2 cases of cystic lesions (Table 2).

3.3. Neoplastic diagnoses

The initial neoplastic diagnoses were as follows: adenocarcinoma (152), metastatic tumors (58), hepatocellular lesions (51), spindle cell tumor (10), lymphoma (7), and poorly differentiated carcinoma (6) (Table 3). All 7 cases of lymphoma showed concordance between initial cytopathologist diagnosis and GI pathologist reexamination; however, those cases were typically also reviewed by hematopathologist. Biopsies of ten spindle cell lesions showed 90% concordance with a single discordant biopsy. In this case, the patient had a prior history of pancreatic adenocarcinoma, the biopsy was initially diagnosed as sarcomatoid carcinoma. Upon reexamination, the lesion showed intersecting fascicles of spindle cells with moderate nuclear pleomorphism and focal weak positivity for cytokeratin (CKAE1/3), influencing the initial diagnosis of sarcomatoid carcinoma. However, additional immunostains stain showed strong, diffuse positivity for SMA, supporting a diagnostic of leiomyosarcoma (Fig. 3).

3.4. Hepatocellular lesions

Hepatocellular processes were mis-identified in only 2 of 51 cases (3.9%), however, both with major discrepancies. Both cases were originally diagnosed as hepatocellular carcinoma, but reexamination and additional immunohistochemical workup revealed metastatic adrenal cortical carcinoma (Fig. 3) and intrahepatic cholangiocarcinoma (Fig. 2), respectively. Regarding the former, the patient had a history of adrenal cortical carcinoma. The core biopsy shows eosinophilic tumor cells with arranged in trabeculae, reminiscent of an HCC. Further immunostains showed the tumor was negative for the hepatocyte marker Hep-par-1, and positive for adrenocortical markers calretinin and Mart-1 (Melan-A), supporting a diagnosis of metastatic adrenal cortical carcinoma. Another discordant case initially diagnosed as HCC showed infiltrating cribriform glands with conspicuous luminal mucin secretion (Fig. 2). The biopsy was initially stained for Hep-Par-1 which showed weak, patchy positivity thus influencing the cytopathologist's original diagnosis. The gastrointestinal pathologist ordered a further immunostain for CK 7, which showed diffuse, strong cytoplasmic positivity. With the combination of morphology and IHC, this case was more in keeping with an intrahepatic cholangiocarcinoma (ICC).

3.5. Metastatic tumors

One hundred and fifty-two cases of adenocarcinoma were included in the study, and the majority of them were metastatic carcinoma with the top three being from the pancreas, coloretum, and breast. The most likely primary sites were determined based on morphology and clinical history (Table 4). Biopsies of adenocarcinoma showed very high concordance rate with 3 minor discordant cases out of 152 total cases (98.0%). Two cases with original diagnoses of “metastatic adenocarcinoma” were refined as metastatic prostatic carcinoma upon re-review (Fig. 4). A third case, in addition to the metastatic adenocarcinoma component, also showed a focus of concurrent well differentiated neuroendocrine tumor (WDNET), as confirmed by strong, diffuse staining for CD56 and chromogranin (Fig. 4).

Among the 58 cases of other types of metastatic tumors, 23 were neuroendocrine neoplasms, 7 each were squamous cell carcinomas, renal cell carcinomas, and melanomas, and 6 were urothelial

Table 3
Summary of total neoplastic cases and discordant neoplastic diagnoses with revised diagnoses by GI pathologist.

Cytopathogist diagnosis	Total cases (%)	Discordant cases (%)	GI pathologist revised diagnosis
Adenocarcinoma	152 (53.5)	3 (1.0)	• 1 with concurrent NET • 2 refined as prostatic Ca
Other metastatic tumor	58 (20.4)	2 (0.7)	• NET, instead of NEC • UC (no cirrhosis), instead of UC with cirrhosis.
Hepatocellular lesion	51 (17.9)	2 (0.7)	• ICC, instead of HCC • ACC, instead of HCC
Spindle cell tumor	10 (3.5)	1 (0.3)	• LMS, instead of sarcomatoid Ca
Lymphoma	7 (2.4)	0 (0)	
Poorly differentiated Ca	6 (2.1)	1 (0.3)	• LCNEC, instead of Poorly differentiated Ca
Total	284 (100)	9 (3.1)	

%: percentage of total neoplastic cases; UC: urothelial carcinoma; Ca: carcinoma; NET: well differentiated neuroendocrine tumor; NEC: Neuroendocrine carcinoma; ICC: intrahepatic cholangiocarcinoma; ACC: adrenal cortical carcinoma; HCC: hepatocellular carcinoma; LMS: leiomyosarcoma; LCNEC: large cell neuroendocrine carcinoma.

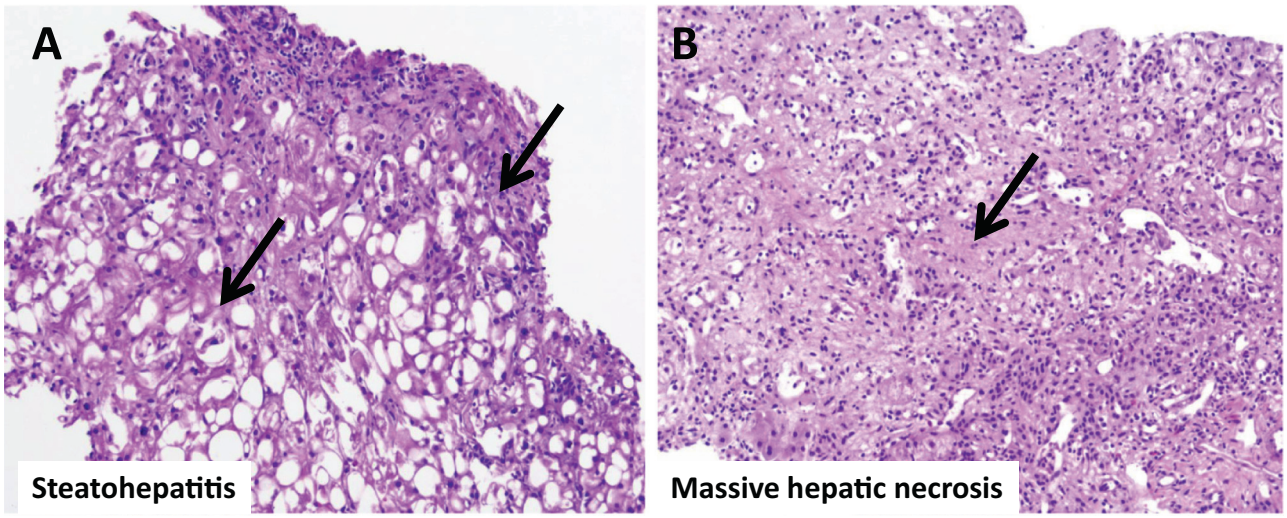

Fig. 1. Discordant biopsies originally diagnosed as non-neoplastic conditions by the cytopathologists. A. Liver biopsy initially diagnosed as "macrovesicular steatosis and mild chronic portal inflammation." The biopsy shows severe macrovesicular steatosis with lobular lymphocytic inflammation and foci of ballooning degeneration (arrow), diagnostic of steatohepatitis. B. Case originally diagnosed as "fibrosing cholestatic hepatitis". On review, extensive area showing complete loss of hepatocytes is seen (arrow), predominately in zones 2–3, with parenchymal collapse and scattered infiltrating lymphocytes. These features are in keeping with massive hepatic necrosis. (A through B, hematoxylin-eosin; original magnifications ×200).

carcinomas. The remaining 8 cases belonged to other rare entities. Of the 2 discordant cases, one metastatic urothelial carcinoma was initially reported to have cirrhosis. Upon re-review, the pattern of fibrosis showed bland spindle or stellate shaped cells embedded in a densely fibrotic collagenous stroma in direct contact with foci of metastatic carcinoma, which is consistent with tumor-induced fibrosis/desmoplasia. The other discordant case was originally called large cell neuroendocrine carcinoma and was reinterpreted as well-differentiated neuroendocrine tumor. This case showed a trabecular arrangement of tumor cells with granular chromatin and round nuclei. Essential diagnostic features of large cell neuroendocrine carcinoma including brisk mitotic activity and extensive necrosis were absent. Upon further evaluation by GI pathologist, Ki-67 stain showed a labeling index of approximately 10–15%, which is more in keeping with a well-differentiated neuroendocrine tumor (Fig. 5). Additionally, one case originally diagnosed as poorly differentiated carcinoma was re-interpreted as large cell neuroendocrine carcinoma based on diffuse CD56 immunostaining (Fig. 5). All cases initially diagnosed as metastatic squamous cell carcinoma, renal cell carcinoma, and melanoma showed concordance between cytopathologist and GI pathologist (Table 3).

3.6. Overall concordance

Overall, the gastrointestinal pathologist and cytopathologist agreed on the diagnosis in 332 of 349 cases (95.1%) with a total of 17 discordant diagnoses (4.9%). Most common discordances were in the diagnosis of neuroendocrine neoplasms, steatohepatitis, fibrosis, HCC, and prostatic carcinoma (Table 5). Major diagnostic discrepancies were rare, observed in only 4 cases (1.1%).

4. Discussion

In the era of a subspecialty pathology service model, the assignment of liver mass core biopsy with concurrent FNA is variable among different institutions. To our knowledge, this is the first study to explore the interpretation of liver mass biopsy between cytopathologist and gastrointestinal pathologist. Through retrospective review of 349 biopsies performed over a 5-year period, we have shown that the gastrointestinal pathologist and cytopathologists had a very high rate of agreement overall (95.1%), especially for neoplastic lesions (96.8%). For diagnosis of non-neoplastic lesions the rate of concordance was somewhat less robust (87.7%). This is in keeping with prior studies which described the challenging nature of non-neoplastic liver pathology which can be prone to higher rate of inter-observer variability [3-5].

In order to ensure diagnostic accuracy, especially regarding non-neoplastic liver disease, non-GI pathologists often seek second opinions from hepatic pathology specialists in difficult cases, and this can reduce the incidence of diagnostic discrepancy. Guidelines have been published recommending that liver biopsies should be reported only by pathologists with extensive experience [6,7]. In addition, studies have reported on the value of GI/liver pathology specialist review of liver biopsies in the diagnosis of neoplastic and non-neoplastic liver disease [3,5]. Some institutions have special protocols for non-neoplastic liver biopsy such as multiple histologic levels or special stains, which may not be done when accessioned to cytopathology. Moreover, many hepatologists expect comprehensive reports of non-neoplastic liver biopsies including detailed microscopic descriptions and synoptic reports, with which non-GI pathologists may not be familiar.

Steatohepatitis was not mentioned in 3 of 9 cases of fatty liver disease (Fig. 1). Patients diagnosed with non-alcoholic steatohepatitis (NASH) have a markedly increased risk of progression to fibrosis compared with simple steatosis [8]. On average, NASH has been reported to progress to fibrosis in 7 years, compared to 14 years with non-alcoholic steatosis [9]. In evaluating cases of steatosis, it is crucial to pay close attention to the features ballooning degeneration, which is the hallmark of hepatocellular injury in steatohepatitis. Ballooning degeneration is characterized by cellular swelling, rarefaction of the hepatocytic cytoplasm and clumped strands of intermediate filaments. Also, Mallory bodies are often found in hepatocytes undergoing ballooning degeneration.

Massive hepatic necrosis (MHN) was missed in one case initially diagnosed as "fibrosing cholestatic hepatitis" (see Fig. 1). Massive hepatic necrosis is characterized by extensive panlobular necrosis, and indicates the likely presence of the clinical syndrome of acute fulminant liver failure. The etiologies of acute fulminant liver failure include acute viral hepatitis, drugs or toxins, autoimmune hepatitis, metabolic diseases, vascular diseases, and malignancies. Acute viral hepatitis is the most common and important cause of acute fulminant liver failure worldwide [10].

Hepatocellular neoplasms are the most common primary neoplasm in the liver and the major clinical diagnosis for a mass lesion. Not

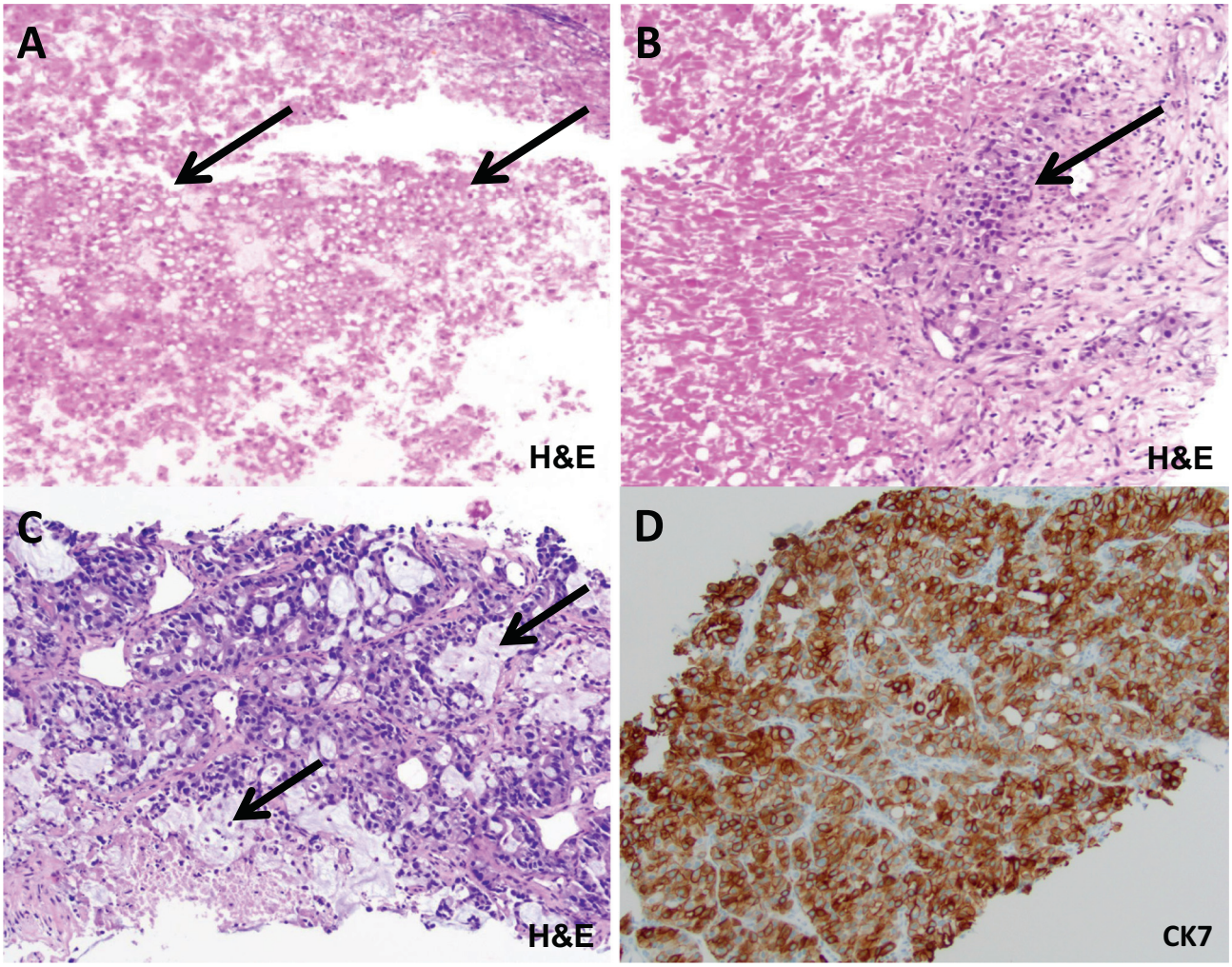

Fig. 2. A and B. Case of HCC with extensive necrosis originally diagnosed by cytopathologist as "Necrosis". H&E stained sections show extensive coagulative necrosis with foci of viable hepatocellular carcinoma (arrows). C and D. Discordant biopsy originally diagnosed as hepatocellular carcinoma by cytopathologist and re-interpreted as intrahepatic cholangiocarcinoma by GI pathologist. C. The invasive tumor shows true glandular differentiation with abundant luminal mucin production (arrow). D. Additional immunostain for CK 7 showed diffuse, strong cytoplasmic positivity, which supports the diagnosis of cholangiocarcinoma, (A and B, hematoxylin-eosin; original magnifications ×400; C, hematoxylin-eosin; original magnifications ×200; D, immunostains counterstained with hematoxylin-eosin, original magnifications ×200).

surprisingly, this category showed a high rate of concordance (94.1%) between cytopathologists and gastrointestinal pathologist with only two (3.9%) cases mis-identified. Cases initially diagnosed as hepatocellular adenoma and focal nodular hyperplasia showed 100% concordance between cytopathologist and gastrointestinal pathologist. These results are reassuring that with sufficient training and experience, cytopathologists can render diagnoses of most common hepatocellular neoplasms with accuracy, without reflexive mandatory consultation with a GI pathologist.

One case of metastatic adrenal cortical carcinoma was mistakenly diagnosed as hepatocellular carcinoma (Fig. 3). Both HCC and adrenal cortical neoplasm show "pink cell" morphology, and HCC can be morphologically similar to adrenal neoplasms due to its trabecular pattern and eosinophilic cytoplasm. Cases of adrenal cortical neoplasms mistakenly diagnosed as have hepatocellular carcinoma have been reported in the literature [11,12]. Adrenal cortical neoplasms in liver parenchyma can be found in one of three scenarios: direct invasion or adhesion to liver parenchyma, tumors arising in adrenohepatic fusion tissue, or in ectopic adrenal gland tissue [12]. If the patient's clinical history is not consistent with hepatocellular carcinoma (i.e. no history of chronic hepatitis or cirrhosis, no elevation of serum alpha fetal protein, etc.) or a clinical history of adrenal mass is given, exclusion of metastatic adrenal neoplasm is in order.

A discordant case was initially diagnosed as HCC but upon review, the tumor showed cribriform glands, abundant mucin, and diffuse positivity for CK7, diagnostic of intrahepatic cholangiocarcinoma (ICC) (Fig. 2). HCC may display focal pseudoglandular architecture but mucin secretion is very uncommon in HCC. Of note, due to a common progenitor cell, there is some overlap in immunophenotype seen in HCCs and ICC. While relatively sensitive for HCC, the hepatocellular stain Hep-Par-1 is not entirely specific, with positive staining in up to 12.5% of ICC [13]. HCC does not show diffuse staining for "biliary type cytokeratins" such as CK7, but focal expression of CK7 can be detected in up to 15% of HCC [14]. Whereas ICC shows diffuse positivity for "biliary type cytokeratins" (CK7 and CK19) and does not strongly express hepatocytic markers (AFP, glypican-3, CK8 and 18, Hep-Par-1). Combined hepatocellular cholangiocarcinoma (HCC-CC) is a rare tumor with histological characteristics of both HCC and cholangiocarcinoma [15,16]. This case lacked histologic features of hepatocellular differentiation, thus ruling out HCC-CC. Differentiation between ICC and HCC can be achieved in most cases based on histologic features and immunohistochemical studies including CK19 or CK7, MOC31, pCEA, and Hep-par-1 [17,18]. However, when lacking extensive liver pathology experience, we recommend that cytologists should consider

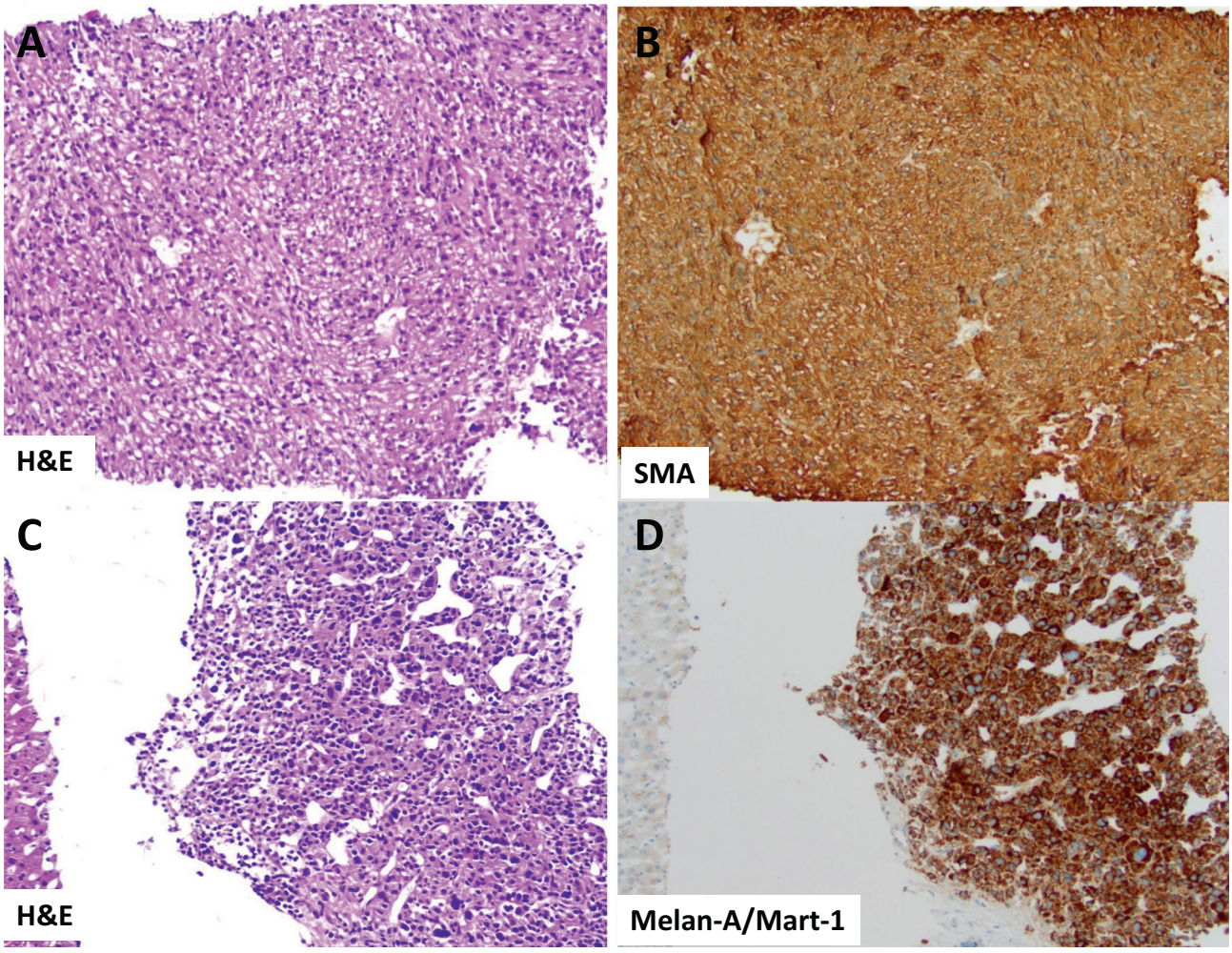

Fig. 3. Cases of malignant neoplasms with discordant diagnoses. A and B. Biopsy initially diagnosed as sarcomatoid carcinoma, where upon reexamination by a GI pathologist, a diagnosis of leiomyosarcoma was rendered. A. By H&E stain, the lesion shows cellular, intersecting bundles of spindle cells with eosinophilic cytoplasm, elongated blunt-ended nuclei, moderate nuclear pleomorphism and occasional mitotic figures. B. An immunostain for SMA showed diffuse, strong cytoplasmic expression, in keeping with a diagnosis of leiomyosarcoma. C and D. Discordant biopsy initially diagnosed as hepatocellular carcinoma by cytopathologist and re-interpreted as adrenal cortical carcinoma by gastrointestinal pathologist. C. The core biopsy shows irregular cords and trabeculae of tumor cells with eosinophilic to clear cytoplasm, moderate nuclear atypia, and occasional mitotic figures. There are also sinusoids, mimicking HCC. D. Strongly positive cytoplasmic staining for Melan-A/Mart-1 and calretinin (not shown), diagnostic of adrenal cortical carcinoma (A, hematoxylin-eosin; original magnifications ×400; B, immunostains counterstained with hematoxylin-eosin, original magnifications ×400; C, hematoxylin-eosin; original magnifications ×200; D, immunostains counterstained with hematoxylin-eosin, original magnifications ×200).

Table 4
Primary sites of adenocarcinoma in the study cohort.

Primary site	# of cases	%[a]
Pancreas	42	27.6%
Colorectum	27	17.8%
Breast	18	11.8%
Liver (ICC)[b]	13	8.6%
Lung	10	6.6%
Extrahepatic biliary tract	8	5.3%
Duodenum	4	2.6%
Ampulla	3	2%
Stomach	3	2%
Prostate	2	1.3%
Uterus	1	0.7%
Urachus	1	0.7%
Unknown/unspecified	20	13.2%
Total	152	

[a] Percentage of the total number of cases of adenocarcinoma (152).
[b] ICC: intrahepatic cholangiocarcinoma.

obtaining liver pathology specialist consultation to discriminate ICC from HCC.

Upon expert reexamination, a spindle cell lesion originally diagnosed as “sarcomatoid carcinoma” was determined to be leiomyosarcoma (Fig. 3). The tumor cells showed weak positivity for cytokeratin (CKAE1/3), influencing the initial diagnosis of sarcomatoid carcinoma. Pathologists should be aware of cytokeratin expression in smooth muscle tumors. One must consider leiomyosarcoma prior to rendering a diagnosis of sarcomatoid or spindle cell carcinoma based solely on cytokeratin or EMA expression alone. “Aberrant” expression of cytokeratins and EMA in leiomyosarcoma has been emphasized as a possible serious pitfall in tumor diagnosis [19,20]. Conventional leiomyosarcomas are almost always metastatic when involving the liver, and search for a primary tumor in locations such as the retroperitoneum is always necessary.

Unexpectedly, the cytopathologists' diagnoses of neuroendocrine neoplasms showed the highest rate of discordance. Out of 23 total cases of neuroendocrine neoplasm, there were 4 discordant diagnoses (17.4% discordance). The possible reasons of mis-interpretation included: failure to perform or over-interpret neuroendocrine marker staining,

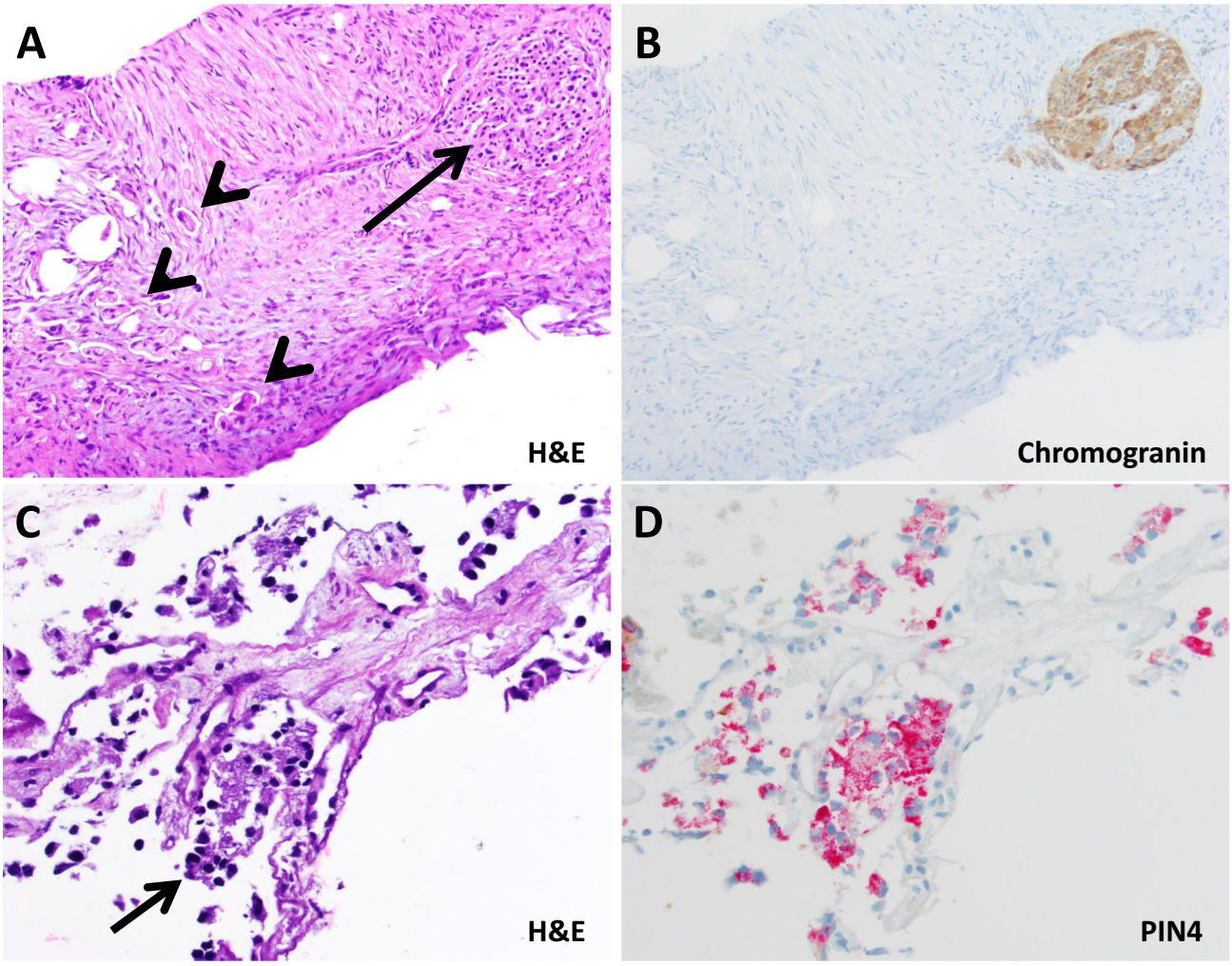

Fig. 4. Cases of metastatic adenocarcinoma with discordant diagnoses. A and B. A case of metastatic adenocarcinoma where a concurrent well differentiated neuroendocrine tumor (WDNET) was missed. A. H&E stain of core biopsy showing fibrotic stroma with a well circumscribed nest of uniform epithelioid cells with round nuclei and granular chromatin located in the upper right corner of the image (arrow). The tumor cells had no mitotic activity or necrosis. The adenocarcinoma is on the left side (arrow head). B. Tumor cells in the upper right corner showed strong, diffuse positive staining for chromogranin. The histologic and immunophenotype features are diagnostic of WDNET. C and D. Case initially diagnosed as "metastatic carcinoma" where upon review, a refined diagnosis of metastatic prostatic carcinoma was rendered. C. H&E stain shows tumor cells in irregular cords and nests with small inconspicuous lumens (arrow). D. Immunostain for PIN4 cocktail shows tumor cells with strong, diffuse racemase (P504S) expression and negative expression of basal cell markers (p63,34βE12). (A and C, hematoxylin-eosin; original magnifications ×400; B and D, immunostains counterstained with hematoxylin-eosin, original magnifications ×400).

failure to keep up with current classifications of neuroendocrine neoplasms, and failure to accurately count mitotic activity or Ki67 labeling index (Fig. 5). Well-differentiated neuroendocrine tumor and poorly differentiated neuroendocrine carcinoma are considered two distinct types of tumors with different pathogenesis, prognosis, and treatment, thus differentiation of poorly differentiated neuroendocrine carcinoma from well-differentiated neuroendocrine tumor and other types of carcinoma has important clinical implications [21].

This study suggests that liver biopsy interpretation is an area where a GI pathology specialist review should be frequently obtained by cytopathologists, especially in non-neoplastic disease such as suspected steatohepatitis, or in staging of fibrosis. Additionally, other studies have recommended GI pathology specialist review of liver biopsies to accurately diagnose other non-neoplastic disease, specifically if biliary disease and autoimmune hepatitis are suspected [3,4,22]. There are studies showing the value of second opinion in regard to non-hepatic diseases and neoplasms [23,24]. These studies have shown that expert second opinions may result in major improvements in clinical treatment and overall cost-effectiveness. Several studies evaluated GI pathology specialist second opinion review of liver biopsies for diagnosis of both neoplastic and non-neoplastic liver disease. Bejarano et al. reported that in 28% liver biopsy specimens, the consultants identified discrepancies in the diagnosis from the original pathologists, which, in the opinion of the consultants, would have a significant impact on the patient management. Reported areas with frequent discrepancies included biliary pathology, staging of fibrosis, and the diagnosis of autoimmune hepatitis [3,22].

5. Conclusion

The overall concordance rate of liver biopsy for mass lesions was very high between cytopathologists and gastrointestinal pathology specialist at an academic, tertiary care hospital. Based on our findings however, we suggest that cytopathologists and general pathologists should consider the use of GI/liver pathology specialist consultation for liver mass FNA and core biopsy in the following situations: discriminate HCC from ICC, diagnosis of neuroendocrine neoplasm, ruling out steatohepatitis, assessment of fibrosis, and certain metastatic carcinoma. Consultation with gastrointestinal specialty pathology may help to improve diagnostic accuracy and optimize patient management.

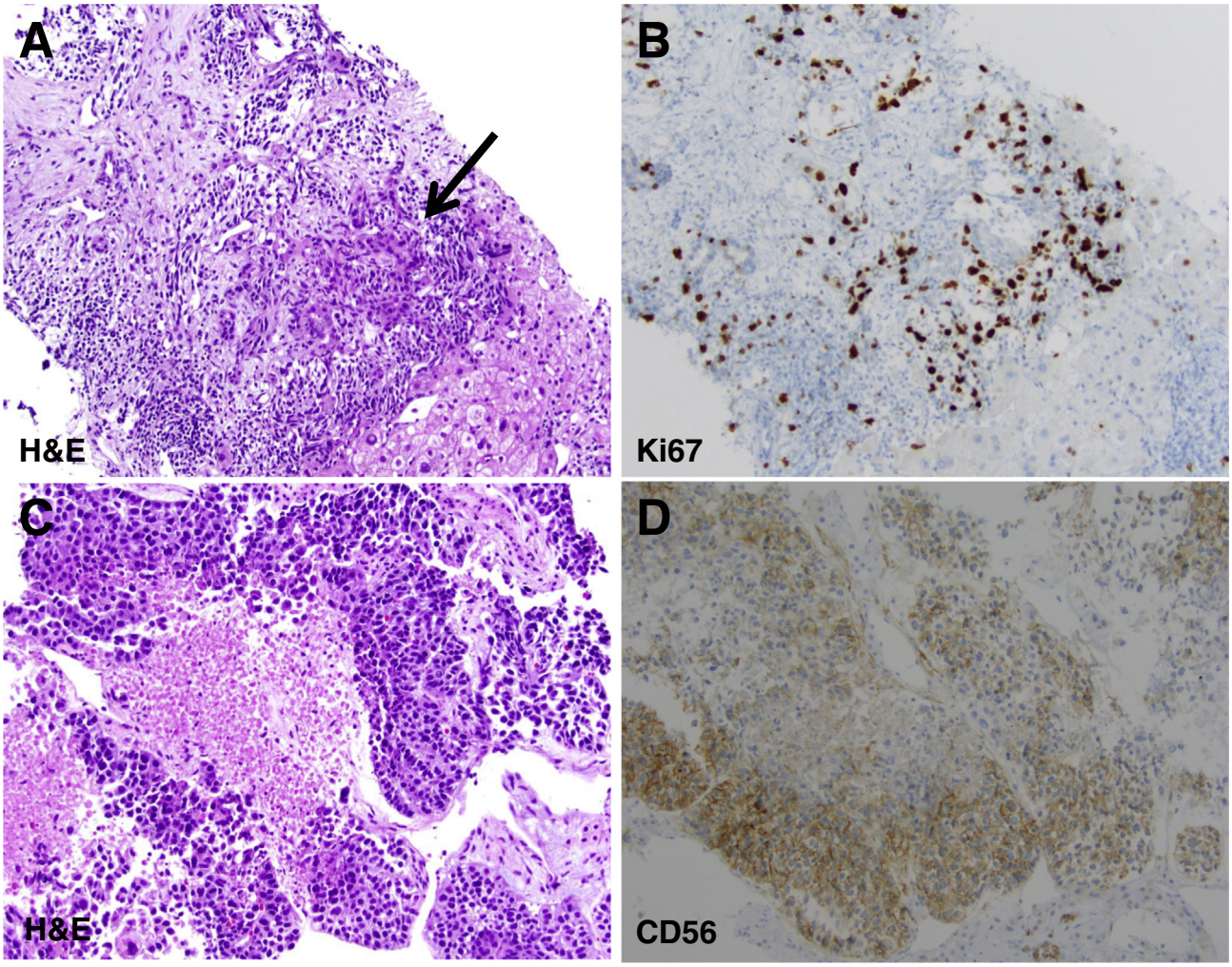

Fig. 5. Neuroendocrine neoplasms mis-characterized by original cytopathologists' diagnosis. A. and B. This biopsy was initially diagnosed as large cell neuroendocrine carcinoma (LCNEC) and determined to be WDNET on reexamination. A. H&E stained sections reveal tumor cells with granular chromatin and round nuclei (arrow) within a nested and trabecular arrangement. Essential diagnostic features of LCNEC were absent, including brisk mitotic activity and extensive necrosis. B. Ki-67 stain shows labeling in approximately 10–15% of tumor cell nuclei, which is consistent with a well-differentiated neuroendocrine tumor (WDNET). C and B. Liver mass biopsy with original cytologist rendered diagnosis of "poorly differentiated carcinoma.", but diagnosed as LCNEC by GI pathologist. C. H&E stained sections show sheets and nests of large tumor cells with abundant eosinophilic cytoplasm, coarse chromatin, nuclear pleomorphism, and prominent nucleoli. High mitotic activity and extensive geographic necrosis are present. D. Subsequent CD56 immunostain showed moderate to strong, diffuse membranous expression in viable tumor cells. The histologic features and CD56 expression supports a diagnosis of LCNEC. (A and C, hematoxylin-eosin; original magnifications ×200; B and D, immunostains counterstained with hematoxylin-eosin, original magnifications ×200).

Table 5
Common discordance between cytopathologist and GI pathologist.

Original diagnostic subcategory	# of cases	%[a]
Neuroendocrine neoplasms	4/17	23.5%
Steatohepatitis	3/17	17.6%
Fibrosis	3/17	17.6%
HCC	3/17	17.6%
Prostatic carcinoma	2/17	11.8%

[a] Percentage of the total number of discordant cases (17).

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