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Original contribution

Identification of key challenges in liver pathology: data from a multicenter study of extramural consults☆,☆☆

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Summary Extramural consultation for challenging pathology cases is an important part of patient care. The specific reasons why liver cases are submitted in consultation are poorly understood. To study patterns in extramural consultation, data were gathered from 1360 liver/GI/pancreatobiliary consults submitted to 7 academic centers. Liver cases comprised 40% of consults and are the focus of this paper. They were submitted for questions on medical (61%) and tumor pathology (39%). A preliminary diagnosis was provided by the referring pathologist in 65% of cases. The most common questions in medical liver pathology were on general classification of a hepatitic pattern of injury (37%), primary biliary cirrhosis (14%), fatty liver disease (13%), autoimmune hepatitis (12%), and etiology of cirrhosis (10%). Most tumor consults were submitted for classification (83%). The most common final tumor consultant diagnoses for benign tumors were hepatic adenoma or focal nodular hyperplasia (52%) and for malignant tumors were metastatic malignancies (47%), hepatocellular carcinoma (32%), or cholangiocarcinoma (8%). For cases submitted with a diagnosis of malignancy, the diagnosis was concordant (43% of cases), concordant but with a generic diagnosis for which a more specific diagnosis could be rendered (37%), or discordant with a major change in diagnosis from malignant to benign or change in tumor type (17%). In conclusion, analysis of consult patterns identifies challenging areas in medical and tumor liver pathology, areas that benefit from consult services and can be focused on by continuing medical educational activities.

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1. Introduction

Extramural consultation serves an important role in patient care. Practicing pathologists have completed full residency and sometimes fellowship training programs. Despite this training, a subset of surgical pathology cases are challenging to interpret and the pathologist remains uncertain about the correct diagnosis. In other cases, the pathologist might have a specific diagnosis or a limited differential in mind, but desires additional expert review to confirm the diagnosis or help prioritize the differential. In addition, clinicians sometimes request a case be reviewed by extramural consultation because of discordant clinical and histological findings.

Data on which types of liver specimens and which types of questions trigger extramural consultation are limited, with most data focusing on diagnostic error rates in submitted material. Yet, data on what types of disease patterns are challenging should be a critical part of the foundation on which post-training courses in continuing medical education are built. Such data can also suggest specific areas where review papers or guideline papers from professional societies may have particularly strong impacts on patient care. In addition, these data are relevant to providing better training in residency and fellowship programs. Finally, these data help the broader pathology community understand which type of challenging cases benefit the most from extramural review.

This study was designed to address these questions through a large multicenter analysis of consult cases submitted to reference medical centers. To best answer these questions, the study focused on key patterns and diagnoses and was not designed to identify small changes between diagnoses, even if they were potentially medically relevant. As one example, differences between a submitted diagnosis and the final consult diagnosis for the grade of inflammation in a liver biopsy was not captured.

2. Materials and methods

After IRB approval, data on cases submitted for consultation were collected from 7 medical centers by nine practicing pathologists. A common data collection sheet was used. The data collection sheet was designed to capture who sent the consult (pathologist, clinician, patient, unclear), what type of information was received with the consult, why the consult was sent, what diagnosis was submitted with the case, and the consultant's final diagnosis. The types of information received with the consult were broadly divided into these categories: clinical information, laboratory test results, and imaging findings. The consultant pathologist determined if relevant information was received and was sufficient. In cases where the diagnosis did not require clinical, laboratory, or imaging findings, missing information was recorded as "not necessary."

Data were collected from sequential consults in the area of gastrointestinal, pancreatobiliary, and liver pathology submitted to the participating centers during the year 2017 to 2018. The exact time frame was not identical in each center, as the goal was to collect data with a target of 100 cases, or more if possible, and consult volumes are center dependent. Data collection started in March of 2017 and the majority of all data were collected, de-identified, and centrally collated by November of 2017. Individual cases were not centrally reviewed. Only data from true consult cases (primary consults) were collected. Data on extramural cases were not collected when cases were reviewed because patients were being treated at the reference hospital (secondary consults).

Data analysis was performed using online SPSS and Excel statistical analysis tools.

3. Results

A total of 1360 consults were entered into the database. Pathologists submitted an average of 151 cases per person (median, 101; range, 65-340). This study focuses on the subset of cases that were liver consults, which consisted of 541 cases (40% of all cases). The vast majority of liver consult cases were needle biopsies (N = 517), with occasional wedge biopsies (N = 9) and resection specimens (N = 15). Most cases were submitted for questions about medical liver interpretation (N = 328, 61%) or for tumor evaluation (N = 213, 39%). For the purposes of data analysis, cases that had been submitted with a medical question but had a final consultant diagnosis of a tumor (N = 3) and biopsies that were targeted towards a mass lesion on imaging but no mass was seen on biopsy (N = 23) were included with tumor consult cases.

3.1. Who sent the consult

The majority of cases were submitted by a pathologist (83%), Table 1. However, clinician directed consults made up a substantial minority of cases (17%). Clinician requested

Table 1 Source of 541 submitted consults

Source	Count
Pathologist	404
Nontumor	227
Tumor	177
Clinician	83
Nontumor	64
Tumor	19
Not available [a]	53
Nontumor	36
Tumor	17
Patient	1
Nontumor	1
Tumor	0

[a] Not available due to data collection error.

Table 2 Age and gender of patients in submitted consult cases

	Consults (N)	Years of age (mean ± SD)	Note
Total	541	56± 17	
M	225	58± 16	M *vs* F age, $P = .002$, student t test
F	264	54± 17	
Not available [a]	52	NA	
Medical consults	328	53± 16	M *vs* F age, P = NS, student t test
M	116	54± 16	
F	177	52± 17	
Not available [a]	35	NA	
Tumor consults	213	61± 16	
M	109	64± 14	M *vs* F age, $P = .003$, student t test
F	87	57± 17	
Not available [a]	17	NA	

[a] Not available due to data collection error.

consults were enriched for medical cases (19%) compared to tumor cases (8%, $P = .0001$).

3.2. Demographics

The average age of male patients was 58 years, modestly higher than for female patients, 54 years (Table 2). The average age of patients with tumor consults was 11 years higher than for medical consults ($P < .001$).

3.3. Information received with consult cases

Information received with the consult was broadly grouped into laboratory tests, clinical information, and imaging findings. Potentially relevant laboratory information was missing in 29% of cases, clinical information in 17% of cases, and imaging results in 43% of cases (Table 3). Tumor consult cases, when compared to medical consults, had a higher frequency of missing information for all of these categories of information (Table 3).

3.4. Submitted diagnoses

A preliminary diagnosis or the signed out diagnosis was submitted with the consult in 68% of all cases (Table 4), though with a higher frequency in tumor cases (73%) than non-tumor cases (64%) ($P = .046$).

3.5. Reasons for submitting medical consults

In 26% of medical consult cases (N = 88), there was no accompanying letter that posed a question and no diagnosis in the submitted pathology report; these cases were classified as being submitted for general interpretation. The final diagnoses in cases that were submitted with no specific question and no diagnosis had a different overall pattern than consults that were

Table 3 Receipt of relevant information with consults

	Received N (% of total)	Not received but not relevant N (% of total)	Cases missing relevant information N (% of total)
All cases, N = 541			
Laboratory test results	303 (56%)	82 (15%)	156 (29%)
Clinical information	433 (80%)	18 (3%)	90 (17%)
Imaging findings	168 (31%)	140 (26%)	233 (43%)
Medical consults, N = 328			
Laboratory test results	261 (80%)	3 (1%)	64 (20%)
Clinical information	276 (84%)	5 (2%)	47 (14%)
Imaging findings	70 (21%)	126 (38%)	132 (40%)
Tumor consults, N = 213			
Laboratory test results	43 (20%)	79 (37%)	91 (43%)
Clinical information	158 (74%)	13 (6%)	42 (20%)
Imaging findings	98 (46%)	14 (7%)	101 (47%)

Table 4 Diagnoses submitted with cases

	Total N (%)	Tumor N	Medical
Total cases	541	213	328
Submitted diagnosis or suggested diagnosis	278 (51%)	119 (56%)	159 (48%)
No diagnosis submitted	135 (25%)	44 (21%)	91 (28%)
Data missing (not collected)	128 (24%)	50 (23%)	78 (24%)

submitted with a question or diagnosis (Table 5), being enriched for cases of fatty liver disease, drug-induced liver injury, biliary disease, vascular disease, and normal or nearly normal biopsies. The reasons for this observation are not clear and may be multifactorial. It is possible that a subset of these cases may have been submitted without substantial prior evaluation, perhaps driven primarily by practice efficiency needs or significant discomfort with liver pathology.

For those consults which posed either diagnostic questions in the letters or which had preliminary diagnoses, the most common findings were hepatitic patterns of injury (32%), followed by various biliary tract and cholestatic liver diseases (21%) and fatty liver disease (13%). Within the category of biliary tract disease, questions on primary biliary cirrhosis (PBC) (also known as "primary biliary cholangitis" by some authors who advocate renaming this disease) were the most common (12%). Other significant categories included questions on the etiologies for cirrhotic livers (8%) and evaluation of post-transplant liver biopsies (8%). Additional recurrent but less common questions, with frequencies of less than 5%, were as follows: fibrosis staging, granulomas, and drug-induced liver injury (Figure A) (Table 5).

Table 5 Nontumor cases (N = 328); main consult question in letter or main disease in submitted diagnosis; cases without a submitted diagnosis or question are listed under the general interpretation column which shows the final consult diagnosis

Disease	Specific question	General interpretation
	Count	Count
Autoimmune hepatitis	41 (17%)	6 (7%)
Hepatitis NOS	37 (15%)	9 (10%)
Fatty liver disease	32 (13%)	23 (26%)
PBC	30 (12%)	6 (7%)
Cause of cirrhosis	20 (8%)	1(1%)
Transplant related	19 (8%)	1 (1%)
Fibrosis staging question	10 (4%)	0
Biliary diseases, not PSC or PBC	9 (4%)	8 (9%)
Granulomas	6 (3%)	4 (5%)
DILI	6 (3%)	8 (9%)
Cholestatic liver injury	6 (3%)	0
PSC	4 (2%)	0
Iron	4 (2%)	0
Vascular disease	3 (1%)	6 (7%)
GVHD	3 (1%)	0
Grade and stage known viral hepatitis	2 (1%)	0
Wilson's disease	2 (1%)	0
Cause of portal hypertension	2 (1%)	0
Normal or near normal liver	2 (1%)	9 (10%)
Dysplastic nodule	1 (1%)	0
Cytoplasmic inclusions	1 (1%)	0
Inadequate biopsy	0	1 (1%)
Chronic viral hepatitis plus another disease	0	2 (2%)
Non-cirrhotic portal hypertension	0	1 (1%)
Abscess, favor	0	1 (1%)
Nonspecific focal scar	0	1 (1%)
Microvesicular pattern of injury	0	1 (1%)
Total	240	88

Abbreviations: NOS, not otherwise specified; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; DILI, drug-induced liver injury; GVHD, graft versus host disease.

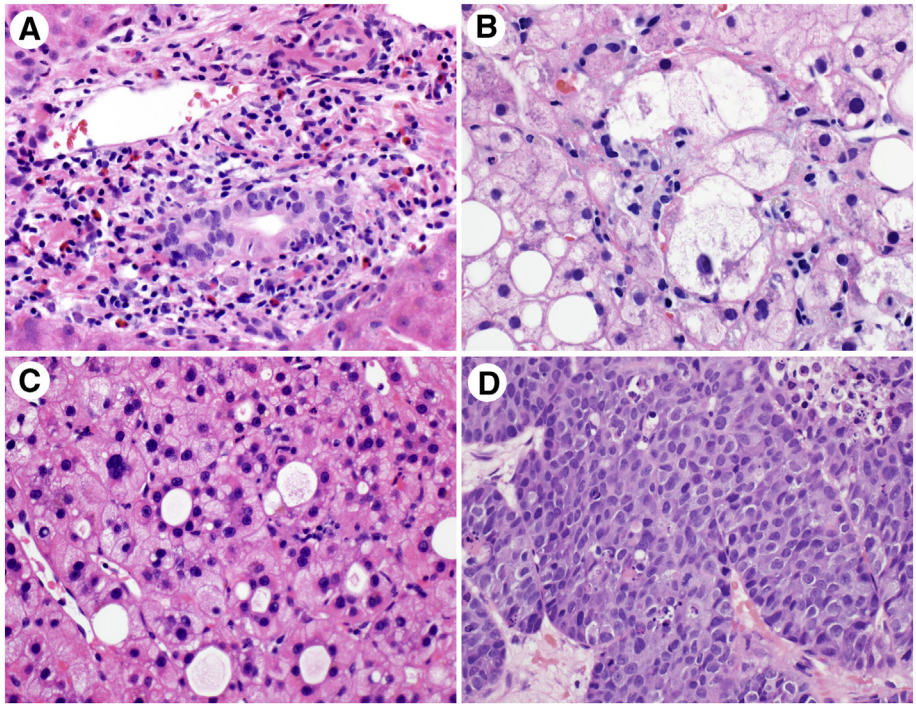

Figure A, Probable Augmentin-induced liver injury. The portal tracts showed mixed portal inflammation with patchy mild bile duct lymphocytosis and injury. The findings were favored to represent drug-induced liver injury, and the patient had a recent history of Augmentin use. B, Steatohepatitis, rule out autoimmune hepatitis. The biopsy shows steatohepatitis. The serum ANA was positive at a titer of 1:160, and the consult was submitted to evaluate for possible autoimmune hepatitis. No features of autoimmune hepatitis were present in the biopsy. C, Hepatocellular carcinoma. This biopsy was submitted to confirm a preliminary diagnosis of hepatocellular carcinoma, which was confirmed by the consultant pathologist as a well-differentiated hepatocellular carcinoma. D, Neuroendocrine carcinoma. A biopsy of a neuroendocrine carcinoma. Neuroendocrine neoplasms were one of the more common types of metastatic disease found in this study.

In addition to requests to confirm a diagnosis of autoimmune hepatitis, consult cases were enriched for ruling out autoimmune hepatitis in the setting of fatty liver disease (Figure B) and for evaluation of overlap syndromes between autoimmune hepatitis and PBC (Table 6). Consult cases also included rare injury patterns such as adult giant cell hepatitis.

Table 6 Types of questions in the setting of autoimmune hepatitis and PBC

Basic question	Main diagnosis considered by referring pathologist	
	Autoimmune hepatitis N	PBC N
Confirm diagnosis	20	17
Overlap, AIH and PBC	8	9
Overlap with PSC	1	3
NAFLD with possible AIH	10	NA
NAFLD with possible PBC	0	1
DILI *vs* AIH	2	NA
DILI *vs* PBC	NA	0

Abbreviations: AIH, autoimmune hepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; NAFLD, Non-alcohol fatty liver disease; DILI, drug-induced liver injury; NA, not available.

Table 7 Subtype information for 73 benign tumors submitted for consultation (based on final consultant diagnosis)

Tumor	Count	notes
Hepatocellular tumors, benign	26	Focal nodular hyperplasia: 10 Hepatic adenoma: 16
Biliary tumors, benign	8	Von Meyenburg complex: 2 Bile duct adenoma: 2 Mucinous cystic neoplasm: 2 Intraductal tubulopapillary neoplasm: 1 Simple biliary cyst: 1
Soft tissue tumors, benign	5	Solitary fibrous tumor: 2 Angiomyolipoma: 2 Hemangioma: 1
Pseudotumors	8	Abscess: 4 Nodular elastosis: 1 Inflammatory pseudotumor: 1 Macroregenerative/dysplastic nodules: 2
Atypical cells, but insufficient for diagnosis	3	
No tumor	23	No histological findings that would explain the mass lesion seen on imaging

Table 8 Subtype information for 140 malignant tumors submitted for consultation (based on final consultant diagnosis)

Tumor	Count	Notes
Hepatocellular tumors, malignant	47	Hepatocellular carcinoma: 45
		Well differentiated: 12
		Moderately differentiated: 6
		Poorly differentiated: 3
		Grade not specified: 23
		Fibrolamellar carcinoma: 1
		Hepatoblastoma: 1
Biliary tumors, malignant	12	Favor cholangiocarcinoma: 10
		Mixed HCC and cholangiocarcinoma: 2
Neuroendocrine tumor	19	WHO grade G1/G2: 5
		WHO grade G3: 7
		Small cell: 5
		Grade not specified: 2
Metastatic, adenocarcinoma	28	No site favored: 9
		Favor pancreatobiliary or upper GI: 8
		Favor colon: 3
		Favor breast: 2
		Favor lung: 2
		Hepatoid: 1
		Adenosquamous: 2
		Mullerian/renal: 1
Metastatic, other	9	Squamous cell carcinoma: 3
		Pancreatic acinar cell carcinoma: 2
		Germ cell tumor: 1
		Melanoma: 2
		Small round blue cell tumor: 1
Lymphoma	3	Diffuse large B cell: 1
		CLL: 1
		Hodgkin lymphoma: 1
Soft tissue tumors, malignant	9	Epithelioid hemangioendothelioma: 4
		Angiosarcoma: 2
		Angiosarcoma *vs* EHE: 1
		Malignant solitary fibrous tumor: 1
		Leiomyosarcoma: 1
Miscellaneous tumors	1	Malignant rhabdoid tumor: 1
Poorly differentiated malignancy, no site of origin identified, could not further subtype	12	Poorly differentiated carcinoma: 8 including 3 carcinoma with sarcomatoid changes
		Poorly differentiated malignancy: 4

3.6. Reasons for submitting tumor consults

The most common benign tumors submitted for consultation were hepatic adenomas and focal nodular hyperplasia (52%), followed by various biliary tumors (16%) and pseudotumors (16%). In another 23 cases, there were no findings in the liver biopsies that would explain a mass lesion, presumably indicating the mass lesion was not sampled (Table 7).

Hepatocellular carcinomas (Figure C) made up 32% of malignant tumors submitted for consultation (Table 8),

Table 9 Outcomes for 287 diagnoses submitted

	Medical N (% column total)	Final diagnosis of benign lesion N (% column total)	Final diagnosis of malignant tumor N (% column total)	Total
Agree	50 (31%)	14 (33%)	37 (43%)	101 (35%)
Disagree	29 (18%)	14 (36%)	15 (17%)	58 (20%)
Change general to specific diagnosis	58 (36%)	11 (28%)	32 (37%)	101 (35%)
Change specific to general diagnosis	2 (1%)	0	0	2 (1%)
Clarification/new finding	23 (14%)	0	2 (2%)	25 (9%)
Total	162	39	86	287

Table 10 Changes in diagnosis involving tumors

Submitted diagnosis	Change in diagnosis (count)	Consult diagnosis
HCC	6	Benign liver: 3 Neuroendocrine tumor: 1 Cholangiocarcinoma: 1 Hepatic adenoma: 1
Various malignant tumors	11	From HCC-CC to HCC: 1 From vascular neoplasm to cholangiocarcinoma: 1 From adenocarcinoma to epithelioid hemangioendothelioma: 1 From adenocarcinoma to lymphoma: 1 Adenocarcinoma, change in site of likely origin: 1 NET, change from G1 to G3: 3 From melanoma to spindle cell malignancy NOS: 1 From adenocarcinoma to ductular reaction: 1 From mucinous cystic neoplasm to polycystic liver disease: 1
Hepatic adenoma	6	Hepatocellular carcinoma: 2 Focal nodular hyperplasia: 1 Solitary fibrous tumor: 1 Angiomyolipoma: 1 Benign liver, no tumor: 1
Focal nodular hyperplasia	1	Hepatic adenoma: 1
Tumor not otherwise specified	1	Hepatic tumor to abscess: 1
Benign injury patterns	3	Hepatic adenoma: 1 Hepatocellular carcinoma: 1 Lymphoma: 1

cholangiocarcinomas 7%, and metastatic epithelial tumors 47%. Most metastatic epithelial tumors were adenocarcinoma or neuroendocrine tumors (Figure D). In 9% of cases, the malignancy was sufficiently poorly differentiated that the tumor could not be fully subtyped and the site of origin was not evident. Lymphomas and soft tissue malignancies made up 9% of all cases.

3.7. Submitted diagnoses versus final diagnoses

While not the primary focus of this study, comparing the submitted diagnoses to the final diagnoses underscores the value of extramural consultation in clinical care. For example, the consultant rendered a more specific diagnosis in 36% of medical liver biopsies, 28% of benign tumor biopsies, and 37% of malignant tumor biopsies (Table 9).

A more detailed analysis was performed on cases with a final consultant diagnosis of hepatocellular carcinoma (N = 45). Of these 45 cases, 7 cases had no submitted diagnosis and data were not collected in 5 cases. Of the remaining 33 cases with a final consultant diagnosis of hepatocellular carcinoma, in 17 cases the consultant diagnosis agreed with submitted diagnosis. In 13 cases, the diagnoses were changed from a submitted general diagnosis, such as "malignant tumor," to a specific diagnosis of hepatocellular carcinoma. In two cases, diagnoses of hepatic adenoma were changed to hepatocellular carcinoma and in one case from a benign granulomatous hepatitis to hepatocellular carcinoma. A separate group of 6 cases were submitted with a diagnosis of hepatocellular carcinoma that was not confirmed by the consultant pathologists (15% of all cases with a submitted diagnosis of hepatocellular carcinoma), with diagnoses changed to benign liver or various types of other tumors (Table 10). Table 10 also shows other changes in submitted diagnoses for benign and malignant tumors.

4. Discussion

Liver consults make up 40% of all GI/liver/pancreas extramural consults in this multicenter study. The majority of liver cases were submitted at the pathologist's request (83%), but clinician requested consults were not uncommon, especially in medical liver cases (19% of cases). The consult material seems to reflect the typical patient seeking medical care, with an average patient-age of 56 years.

In published studies on consult material that included all types of specimens, those from the GI and liver are consistently one of the most frequent types of consults [1]. The current study identifies recurrent challenging areas in liver pathology, providing a comprehensive resource for high yield topics for CME and other educational activities. Several of the strengths of this study include its multi-institutional nature and its focus on primary consult cases, in contrast to secondary consult cases reviewed because a patient was seen at the hospital. This latter group of cases has been analyzed in prior studies and found major discrepancy rates that range from less than 1% to 7% [1-4]. The frequency of major discrepancies in any

given study depends in part on how a major discrepancy is defined, but larger studies tend to find frequencies at the lower end of this range, around 1% to 2%. This frequency for discrepancies is broadly similar to that seen when all specimens at a hospital are secondarily reviewed. For example, one study had each pathology case (N = 3000) reviewed independently by two pathologists and found a major discrepancy rate of 1% [5]. Other studies have combined primary liver consults plus cases reviewed because of patient referral (secondary consults); these studies find a higher frequency of discrepancies, averaging about 40% [6,7].

When there are discrepancies between the initial diagnosis and the consultant diagnosis, a relevant question is which diagnosis is the most correct. Studies have addressed this question by tracking cases over time to determine the most correct diagnosis based on subsequent clinical findings, radiology findings, natural disease history, or follow up pathology specimens. These data suggest that the consultant diagnosis is correct in 65% of FNA specimens [8] and 85% to 95% of surgical biopsy specimens [1,2,9]. In many cases, the consultant diagnosis is incorrect because of incomplete or misleading information submitted with the biopsy specimen [9]. In the current study, clinical, laboratory, or imaging information that was potentially relevant to the case was submitted in most medical consult cases, but was missing or incomplete in up to 47% of tumor consult cases.

The data from this study do not allow clarification on why so many consults were missing potentially relevant information. Possibilities include a lack of information available to the referring pathologists, or the belief that such information was largely irrelevant to specimen interpretation. Perhaps supporting the latter possibility, tumor consult cases were more likely than medical consult cases to be submitted with a diagnosis or provisional diagnosis. Some of these observations might also reflect consult referral practices, where some centers may wait to send additional information when it is requested by the consultant pathologist, as opposed to sending it up front. In any case, these observations highlight the need for improvements in submitting relevant clinical, laboratory, and imaging findings with consult cases.

Most discrepancies identified by studies of secondary consults tend to fall into the category of providing a more specific medical diagnosis, such as changing an original diagnosis of nonspecific hepatitis to one that favors a specific etiology, changes in fibrosis stage, or changes in tumor classification [3]. In contrast, this study focused on primary consults, generating data on major diagnostic challenges that were recognized by either the clinician or the pathologist to be potentially clinically significant. With this approach, a clear pattern emerges on challenging areas in liver pathology. The most common patterns of injury in medical liver specimens were hepatitic patterns of injury and fatty liver disease. Common challenges included identifying autoimmune hepatitis, overlap syndromes, and ruling out autoimmune hepatitis when patients with fatty liver disease also have positive autoantibodies. Other single center studies have also identified autoimmune hepatitis as a recurrent diagnostic challenge and also found obstructive biliary disease, vascular disease, and fibrosis staging to have high discrepancy rates between original and consultant diagnoses [7,10]. One possible reason for the lower frequency of questions on obstructive biliary tract disease in the current data may be increased reliance on imaging findings by clinical teams to evaluate for biliary tract obstruction. In contrast, a diagnosis of PBC commonly involves liver biopsy.

In conclusion, this multicenter study of primary extramural consultations demonstrates that consults are an important part of patient care. Detailed analysis of consult patterns identifies challenging areas in medical and tumor liver pathology. These challenging areas often benefit from consult services, as evidenced by the high frequency of more specific diagnoses and corrected diagnoses generated by the consultant pathologists. In addition, these data provide high yield topics for continuing medical educational activities.

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