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Cholangitis Lenta

A Clinicopathologic Study of 28 Cases

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Abstract: Cholangitis lenta, also known as ductular cholestasis, cholangiolar cholestasis, or subacute nonsuppurative cholangitis, is an uncommon type of cholangitis characterized by ductular reaction with inspissated bile in dilated ductules. The literature on this unique entity has been limited to only a few studies based on a very limited number of cases, which importantly suggest an association with sepsis and/or intra-abdominal infection. The clinical, laboratory, and histologic features of 28 cases of cholangitis lenta are herein investigated. Twenty-five (89.3%) patients were liver transplant recipients. Most notably, the majority of patients showed clinical signs and symptoms of sepsis, and positive microbiology cultures were demonstrated in 24 (85.7%) patients. Significantly, 15 (53.6%) patients died during their hospitalization, ranging from 2 days to 5 months after the initial liver biopsy that showed histologic features of cholangitis lenta. Among the 13 discharged patients, including 2 who received retransplantation, 4 (14.3%) subsequently died of pneumonia, graft dysfunction, or fungal infection within 7 months to 9.3 years. Only 9 (32.1%) patients were alive at the last follow-up, with the follow-up time ranging from 3.8 to 10.4 years. Our data show that the finding of cholangitis lenta on liver biopsy is thus frequently associated with sepsis and with a high mortality rate. Therefore, accurate diagnosis of this condition on liver biopsy is imperative as it is an indication that the patient may have a potentially life threatening condition that requires immediate medical attention and management.

Key Words: cholangitis lenta, sepsis, ductular cholestasis, cholangiolar cholestasis, cholangitis

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Cholangitis lenta, also known as ductular cholestasis, cholangiolar cholestasis, or subacute nonsuppurative cholangitis, is a unique histopathologic pattern of cholangitis that has been described primarily in septic patients.[1–5] It has also been observed in a small subset of patients with obstructive jaundice.[5,6] The characteristic histopathologic features of cholangitis lenta are proliferation of bile ductules at the periphery of portal tracts, presence of inspissated bile within dilated ductules, and relatively unremarkable interlobular bile ducts.

The term cholangitis lenta was first coined by Schottmuller[7] in 1921, which was considered to be a hepatic analog of an indolent cardiac infection by *viridans streptococci*. The term subacute nonsuppurative cholangitis was first used by Lin et al[5] in their publication in 2007. Once thought to be largely because of mechanical biliary obstruction, this entity is now believed to reflect a more aggressive clinical picture in septic patients. However, the pathophysiologic mechanisms leading to this form of liver injury are not entirely clear, with questions remaining about its relationship to infection, sepsis, and liver transplantation, as well as its clinical implications.

In this study, we reviewed the largest cohort of patients with cholangitis lenta studied to date in order to further characterize the clinicopathologic features of this entity. We attempted to elucidate the relationship between cholangitis lenta to various clinical factors, including laboratory tests, signs and symptoms of sepsis, and liver transplantation status. We also detailed the clinical outcomes of these patients.

MATERIALS AND METHODS

Patients

After approval by the Internal Review Board of our institution (the University of California, Los Angeles), we retrospectively searched our pathology information system to identify liver biopsies that carried the potential diagnosis of cholangitis lenta. A variety of diagnostic phrases and combinations of histologic descriptions were used to maximize the search results. These included "cholangitis lenta," "ductular cholestasis," "cholangiolar cholestasis," "subacute nonsuppurative cholangitis," "ductular reaction and cholestasis," "ductular proliferation and cholestasis," "ductular reaction and inspissated bile," and "dilated ductules and cholestasis." Seventy-five potential cases spanning over a period of 10 years were initially identified based on the diagnosis or microscopic description in pathology reports.

Evaluation of Liver Biopsy Histopathology

Hematoxylin and eosin–stained slides were available for review for all 75 potential cases, along with special

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TABLE 1. Clinical and Laboratory Findings in Patients With Cholangitis Lenta

Patient	Age (y)	Sex	Race	Temperature, Maximum (°C)	AST (IU/L)	ALT (IU/L)	ALP (IU/L)	T-Bili (mg/dL)	WBC ($\times 10^3/\mu L$)
1	42	M	AA	38.0	2575	1015	352	11.8	45.2
2	59	M	W	36.9	2404	1744	421	39.0	15.4
3	15	M	H	38.2	74	52	122	7.0	43.0
4	59	F	NA	38.0	134	95	177	15.2	49.0
5	59	M	W	36.2	394	451	357	4.1	5.6
6	56	M	W	37.9	322	270	719	37.1	20.2
7	61	F	W	37.7	119	423	111	17.8	6.3
8	29	F	A	38.5	95	333	427	13.7	9.7
9	53	M	W	37.4	154	43	204	5.2	18.1
10	65	F	AA	37.7	2790	1360	195	40.4	19.8
11	62	M	H	37.9	1088	467	2152	39.4	31.1
12	41	M	H	39.0	78	170	161	17.2	19.1
13	56	F	H	37.3	15,388	9272	2221	25.9	17.0
14	54	M	H	38.0	48	75	68	3.0	6.8
15	58	F	AA	38.4	301	269	1096	18.0	12.5
16	66	M	W	37.5	99	84	413	38.3	42.0
17	61	M	W	37.4	126	142	481	1.6	8.4
18	3	F	W	39.1	236	91	247	11.2	47.2
19	14	M	W	38.5	77	113	149	1.7	18.1
20	60	F	W	37.8	87	203	260	13.4	23.2
21	52	M	W	39.3	116	101	291	14.3	7.5
22	36	F	H	37.7	47	49	981	2.1	11.2
23	85	F	W	37.3	322	170	638	8.2	20.4
24	68	M	A	38.4	492	132	122	42.5	10.1
25	59	M	W	38.4	60	48	171	24.2	23.83
26	18	M	H	39.4	96	237	123	6.8	33.04
27	62	M	W	38.3	745	626	1010	43.0	21.5
28	65	M	W	37.4	1162	513	267	46.0	16.21

A indicates Asian; AA, African American; ALP, alkaline phosphatase (normal range, 45 to 115 IU/L); ALT, alanine transaminase (normal range, 7 to 55 IU/L); AST, aspartate transaminase (normal range, 8 to 48 IU/L); F, female; H, Hispanic; M, male; NA, not available; T-Bili, total bilirubin (normal range, 0.1 to 1.0 mg/dL); W, white; WBC, white blood cell count (normal range, 4.5 to $11.0\times10^3/\mu L$).

stains for trichrome, reticulin, periodic acid-Schiff (with and without diastase), and iron. The biopsy specimens were reviewed by 2 pathologists, both specialized in liver pathology (B.V.N. and H.L.W.). They were blinded to the clinical parameters and prior rendered diagnoses in order to confirm the diagnosis of cholangitis lenta. Diagnostic criteria included the following: proliferation of bile ductules at the edges of portal tracts, inspissated bile within dilated bile ductules, and no bile accumulation in interlobular bile ducts. A total of 28 cases fulfilled the histologic criteria for cholangitis lenta and were included in the study. The remaining 47 cases did not meet the above diagnostic criteria mainly because of lack of apparent ductular dilatation and lack of characteristic inspissated bile in dilated ductules. Cirrhotic livers with marked canalicular, cytoplasmic, and ductular cholestasis were also excluded from the study because the findings were believed to represent decompensated end-stage chronic liver disease.

Clinical Variables and Infectious Disease Parameters

Detailed clinical information was obtained by review of the electronic medical records for each patient. Demographic data (age, sex, and race), clinical presentations, and other significant clinical conditions were recorded. Laboratory data included serum concentrations of aspartate transaminases, alanine transaminases, alkaline phosphatase, and total bilirubin. Other variables reviewed included maximum body temperature and white blood cell counts during the course of hospitalization. The infectious disease work-up was also reviewed for each case, which included results of blood, urine, respiratory tract, wound, and body fluid cultures. Pertinent radiologic studies were reviewed for the presence or absence of intra-abdominal abscess, biliary obstruction, abnormalities of hepatic vasculature, or other signs of infection. The time frame between the onset of clinical conditions and liver biopsy was recorded.

The clinical outcomes were then investigated for each case. This included either death or discharge home after hospitalization, as well as the condition of survived patients after discharge. When performed, follow-up liver biopsies, explants of retransplantation, or autopsy results were reviewed.

RESULTS

Clinical and Laboratory Findings

Of the 28 confirmed cases of cholangitis lenta, 18 patients were male and 10 were female. The patients ranged in age from 3 to 85 years (mean, 51 y; median, 58.5 y). All but one of the patients had a history of acute onset of illness or were status post abdominal operation. Elevated liver function tests, leukocytosis, fever, and fatigue were the most common clinical presentations. Other documented clinical findings included lethargy, jaundice, ascites, abdominal pain or distension, acute liver failure, encephalopathy, coagulopathy, respiratory distress, renal insufficiency, hyponatremia,

and hypotension. Of particular note, 25 (89.3%) patients were liver transplant recipients and the majority of these patients were recently transplanted (within 11 to 60 d). Only 2 patients (cases 14 and 22) were transplanted >100 days before liver biopsy that showed features of cholangitis lenta. Furthermore, 18 (64.3%) patients developed cholangitis lenta within 30 days after initial liver transplantation.

As shown in Table 1, all patients showed abnormal liver tests during the course of their hospitalization. Specifically, 26 (92.9%) showed elevated aspartate transaminase levels, 24 (85.7%) showed elevated alanine transaminase levels, 26 (92.9%) showed elevated alkaline phosphatase levels, and all (100%) had elevated total bilirubin levels. In addition, 22 (78.6%) patients had elevated white blood cell counts.

Infectious Disease and Radiologic Findings

Table 2 outlines the results of the infectious disease work-up for each patient, including the culture results, the presence or absence of intra-abdominal infection, and the presence or absence of a clinical diagnosis of sepsis. Positive cultures from blood, respiratory tract, body fluids, and wounds were demonstrated in 24 (85.7%) patients. Of note, one of the patients with negative cultures had a perinephric abscess and positive wound cultures 6 months before the initial liver biopsy (case 22), and another case had positive blood cultures 108 days after initial biopsy (case 17). The majority of patients were on a combination of antibiotic, antifungal, and antiviral medications, including one of the case with negative culture results (case 19). Nine (32.1%) patients also had intra-abdominal infections or abscesses. The most common bacterial isolates from blood cultures were *Enterococcus* species (particularly *Enterococcus faecium* and vancomycin-resistant *Enterococci*) and coagulase-negative *Staphylococci*. The most common fungal isolates were *Candida* species. Clinical signs and symptoms of infection were common among patients with cholangitis lenta, as evidenced by low-grade to high-grade fever and leukocytosis seen in the majority of patients (Table 1). Of the 28 cases included in the study, 24 (85.7%) met the clinical criteria for sepsis defined by the American College of Chest Physicians/Society of Critical Care Medicine in 1991, which required 2 or more of the following conditions as a result of infection: temperature >38 or <36°C; heart rate >90 beats/min; respiratory rate >20 breaths/min or partial pressure of carbon dioxide of arterial blood <32 mm Hg; and white blood cell count >12,000, <4000/mm^3, or >10% immature bands.[8] The majority (18/24; 75%) of patients presented with the symptoms and signs of sepsis or showed positive cultures within 1 to 2 weeks before or after liver biopsies. As aforementioned, 3 additional cases had either a perinephric abscess a long time before liver biopsy (case 22), sepsis a long time after liver biopsy (case 17), or likely treated sepsis (case 19). The only case that did not have clinical evidence of sepsis or intra-abdominal infection/abscess (case 7) was a 61-year-old female who presented with persistent hyperbilirubinemia after liver transplantation for hepatitis C cirrhosis. Liver biopsy performed 10 days after transplantation in this patient showed features of cholangitis lenta. Biliary obstruction and ischemic injury were suspected but these possibilities were ruled out upon further clinical and radiographic investigations.

Radiologic imaging, including ultrasound, computed tomographic scan, and magnetic resonance imaging, was examined to determine a number of variables including the presence or absence of intra-abdominal infection or abscess, and the presence or absence of biliary obstruction and hepatic artery thrombosis. After a thorough evaluation of the imaging history for each patient, no patient was found to have evidence of biliary obstruction or hepatic artery thrombosis.

Liver Biopsy Findings

The spectrum of histopathologic findings in the liver biopsies is summarized in Table 3 and exemplified in Figures 1–4. Liver biopsies contained 6 to 46 portal tracts (mean, 19; median, 17). The observed histologic findings included minimal to moderate portal inflammation in all cases, with 7 (25%) cases exhibiting minimal portal inflammation, 20 (71.4%) exhibiting mild portal inflammation, and 1 (3.6%) exhibiting moderate portal inflammation. The portal infiltrates consisted predominantly of lymphocytes with a minimal to mild amount of neutrophils. A few cases also had a minimal amount of scattered eosinophils (5/28; 17.9%) and plasma cells (6/28; 21.4%). Portal edema was not a frequent finding, seen in only 5 (17.9%) cases, and was usually only minimal to mild when present.

Another common finding was bile duct injury, which was present in all but 1 case (96.4%) and was usually minimal to moderate in degree. No inspissated bile or neutrophils were observed within the lumens of bile ducts. Although by definition ductular reaction, dilatation, and cholestasis with inspissated bile were present in every case, mild to marked canalicular cholestasis was also present in the lobules in the majority (20/28; 71.4%) of cases. Other common findings included varying degrees of hepatocyte necrosis/apoptosis (19/28; 67.8%), hepatocyte ballooning (21/28; 75.0%), and steatosis (19/28; 67.8%). Steatosis was predominantly small droplet and microvesicular, typically involved less than one third of hepatocytes, and did not appear to have an apparent zonal distribution. Only 1 case (case 17) involved more than one third (but less than two thirds) of hepatocytes, with a significant fraction of large droplet steatosis. Hepatocyte ballooning appeared to be more commonly observed in zone 3 and more frequently seen in cases with lobular cholestasis, and did not appear to be associated with steatosis as seen in the setting of steatohepatitis. Less frequent findings included lobular inflammation (10/28; 35.7%), which was usually minimal if present, and centrilobular damage (15/28; 53.6%), which we defined as hepatocellular pallor at zone 3 with or without cholestasis for this study. No features of abscess or infectious agents were demonstrated in these biopsies.

Examination of iron stains revealed that the majority (19/28; 67.8%) of cases had a minimal to mild amount of iron deposition, predominantly in Kupffer cells. Reticulin stains revealed at least a minimal degree of

TABLE 2. Infectious Disease Work-up in Patients With Cholangitis Lenta

Case	Culture Results	Intra-Abdominal Infection	Clinical Sepsis	Time Frame Between Onset of Sepsis or Positive Culture Results and Biopsy
1	Blood: *Pseudomonas aeruginosa*; peritoneal fluid: VRE and *Candida* species	+	+	3 d
2	Blood: *Enterococcus faecium*; respiratory tract: *Candida parapsilosis*; wound: gram-positive cocci in pairs and chains	−	+	4 d (after biopsy)
3	Blood: coagulase-negative *Staphylococci*; peritoneal fluid: *Candida* species and *Ralstonia pickettii*	+	+	3 d (after biopsy)
4	Intra-abdominal abscess: VRE; wound: *P. aeruginosa*; fascia: *Candida* and *Enterococcus* species	+	+	12 d (after biopsy)
5	Blood: VRE; respiratory tract: *Enterobacter aerogenes* and *Streptococcus pneumoniae*	+	+	13 d (after biopsy)
6	Blood: *Enterococcus* species and *P. aeruginosa*; respiratory tract: lactose-negative gram-negative rods	−	+	3 d
7	—	—	—	NA
8	Blood: coagulase-negative *Staphylococci*; wound: *Staphylococcus aureus*; bile: *Enterococcus* species; urine: *P. aeruginosa*	−	+	34 d
9	Blood: *E. faecium*; intra-abdominal abscess: *Escherichia coli*; respiratory tract: *P. aeruginosa*; urine: Candida guilliermondii	+	+	Same day
10	Blood: *Enterobacter cloacae*, *C. parapsilosis*, and CMV; respiratory tract: *E. cloacae*, coagulase-negative *Staphylococci*, and lactose-positive gram-negative rods	−	+	3 d
11	Blood and CSF: VRE; respiratory tract: *Citrobacter freundii* and *Candida krusei*; bile and wound: *C. freundii*	+	+	2 d
12	Blood: *S. aureus*; respiratory tract: *S. aureus*, VRE, and *Candida albicans*; urine: *C. albicans*	−	+	4 d
13	Blood: coagulase-negative *Staphylococci*; respiratory tract: *C. albicans*	−	+	1 d
14	Blood: coagulase-negative *Staphylococci*, *E. faecium*, *Klebsiella oxytoca*, and *Candida glabrata*; respiratory tract: *P. aeruginosa*, *S. aureus*, lactose-negative gram-negative rods, and *C. albicans*; urine: coagulase-negative *Staphylococci*, *C. albicans*, and *C. glabrata*; wound: *C. albicans*	−	+	7 d (after biopsy)
15	Blood: *E. coli*; respiratory tract: *S. aureus*, *Stenotrophomonas maltophilia*, and lactose-negative gram-negative rods; bile and wound: *S. maltophilia*	+	+	Same day
16	Blood: *Serratia marcescens* and *E. faecium*; respiratory: *S. marcescens*, *E. coli*, and *C. albicans*; urine: *Enterococcus* species and *C. albicans*	−	+	13 d (after biopsy)
17	—	—	—	NA
18	Blood: *E. faecium* and *C. parapsilosis*; respiratory tract: *C. parapsilosis*	−	+	16 d
19	—	—	+?	3 d
20	Blood: *E. faecium* and *C. glabrata*; urine: *C. glabrata*; respiratory tract: *Aspergillus fumigatus* and *C. glabrata*; wound: *Klebsiella pneumonia* and *C. glabrata*	+	+	6 d
21	Blood and bile: VRE; urine: *E. coli* and *C. albicans*; respiratory tract: *C. albicans*	−	+	21 d
22	—	—	—	NA
23	Respiratory tract: *E. aerogenes* and *C. albicans*; urine: *P. aeruginosa* and *C. albicans*	−	+	9 d
24	Blood: *S. aureus* and *E. faecium*; urine: *S. aureus*, *K. pneumoniae*, and *S. marcescens*	−	+	15 d
25	Blood: *K. pneumoniae* and *C. glabrata*; intra-abdominal abscess: VRE and *C. glabrata*; respiratory tract: *C. glabrata*, *Acremonium* species, and *Enterococcus* species	+	+	44 d
26	Blood and bile: coagulase-negative *Staphylococci*; respiratory tract: *C. parapsilosis*	−	+	8 d
27	Blood and respiratory tract: *S. marcescens*; wound: *K. pneumoniae*	−	+	6 d
28	Blood and urine: *K. pneumoniae*; respiratory tract: *K. pneumoniae* and *C. glabrata*	−	+	19 d

− indicates negative results; +, positive result; CMV, cytomegalovirus; CSF, cerebrospinal fluid; VRE, vancomycin-resistant *Enterococci*.

nodular regeneration in 12 (42.9%) cases. Trichrome stains showed some degree of fibrosis in 13 (46.4%) cases, which was usually periportal, portal, and perisinusoidal in distribution. Portal-to-portal bridging fibrosis was observed in only 2 cases and was focal in both cases.

Clinical Outcomes and Follow-up Findings

Follow-up liver biopsies were available for 14 patients (Table 4). The time interval between initial biopsy and follow-up biopsy ranged from 6 to 157 days (mean, 43.3 d; median, 30.5 d). Two patients (cases 3 and 5) had retransplantation

TABLE 3. Histopathologic Findings of Cholangitis Lenta

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Portal inflammation	++	++	+	++	++	++	++	++	++	++	++	++	++	++	++	++	++	+++	+	++	+	+	++	++	+	+	+	++
Lymphocytes	++	+	+	+	+	+	++	+	+	++	++	+	+	+++	++	+	++	+++	+	+	+	+	++	++	+	+	+	+
Neutrophils	+	++	+	++	++	++	++	++	++	++	+	++	++	+	++	++	+	+	+	++	+	+	+	+	+	+	+	++
Eosinophils	+	−	−	+	−	−	+	+	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−
Plasma cells	+	−	−	−	−	−	−	−	−	−	−	−	−	+	+	−	−	−	−	−	+	−	+	+	−	−	−	−
Portal edema	+	−	−	−	−	−	−	−	−	−	_	−	−	−	++	+	_	−	++	−	+	−	−	−	−	−	−	−
Bile duct injury	++	++	+++	++	+	++	++	++	++	++	+	+	+	++	++	++	+	+	++	++	++	++	++	−	+	++	++	+++
Lobular inflammation	−	−	+	−	−	−	+	−	+	−	−	−	+	+++	_	−	++	−	−	−	+	−	+	_	−	+	−	+
Hepatocyte necrosis	−	+	+++	−	+++	+	+	+	−	+++	−	+	++	+++	+	−	+	+	−	++	+	−	−	++	−	+	++	++
Hepatocyte ballooning	++	+	+++	+	++	−	+++	++	−	++	+	−	++	−	++	++	+	++	−	+++	+	−	+++	+++	−	++	+++	++
Centrilobular damage	−	−	−	−	++	++	−	++	−	++	+	−	++	++	+++	++	−	−	−	+++	++	++	++++	−	++	−	−	++
Sinusoidal dilatation	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	++	−
Canalicular cholestasis	−	+++	+++	++	−	−	++	+++	−	−	+	−	+++	++	+++	++	−	++	+++	+++	++++	−	+++	+++	++	+++	+++	++
Steatosis	+	+	+	+	−	+	−	−	++	+	+	+	++	++	+	++	+++	−	−	+	+	−	++	−	−	−	+	+
Endotheliitis	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	N
Central perivenulitis	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mallory-Denk bodies	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	Y	N
Iron deposition	−	++	+	+	++	+	+	+	++	−	−	−	−	++	++	−	−	−	−	+	+	++	+	+++	+	++	++	++
NRH-like change	N	N	N	Y	N	N	Y	Y	N	Y	Y	N	Y	Y	N	N	N	N	N	Y	Y	Y	Y	Y	N	N	N	N
Fibrosis																												
Bridging	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N
Periportal	Y	Y	Y	Y	Y	N	N	N	N	Y	Y	Y	N	N	Y	N	N	N	N	N	Y	N	Y	Y	N	N	N	N
Portal	Y	Y	Y	Y	Y	N	N	N	Y	N	N	Y	N	N	Y	N	N	N	N	N	N	N	N	Y	N	N	N	N
Perisinusoidal	Y	Y	Y	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y	N	N	N	N

− indicates none; +, minimal; ++, mild; +++, moderate; ++++, marked; N, no; NRH, nodular regenerative hyperplasia; Y, yes.

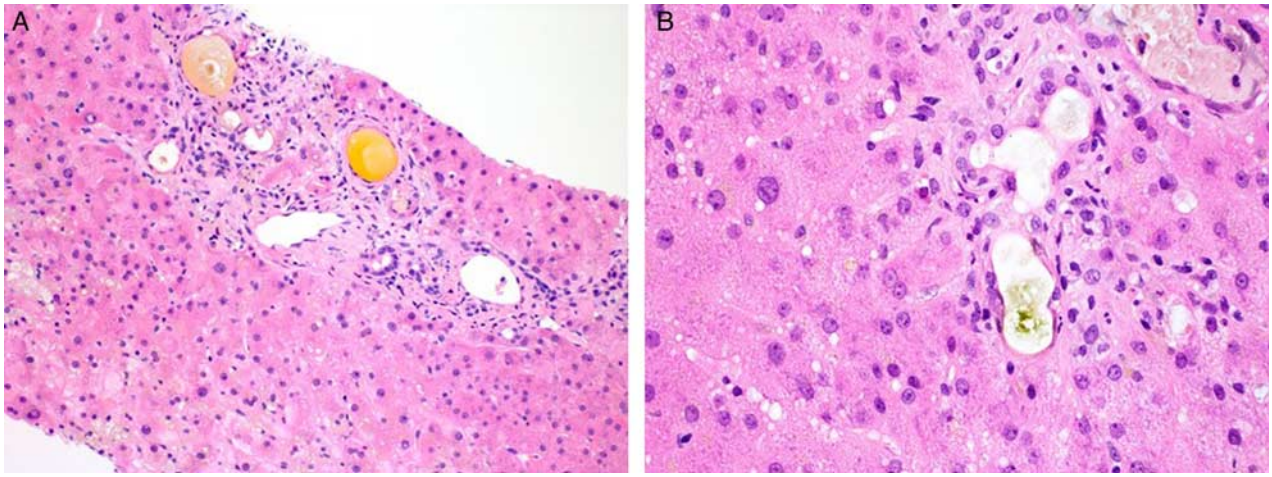

FIGURE 1. A case of cholangitis lenta showing minimal inflammatory cell infiltrates with neutrophils in a portal tract. Portal edema is not evident. A, Inspissated bile is present in dilated bile ductules. Minimal steatosis is noted in the lobules, which is better illustrated in (B).

within 1 month after initial diagnosis of cholangitis lenta on allograft biopsy. Histopathologic examination of follow-up biopsies and explants yielded variable findings, ranging from resolved or minimized cholangitis lenta to persistent cholangitis lenta to more significant hepatocyte injury with necrosis. There was no significant progression in terms of fibrosis. Autopsy results were available for 3 patients (cases 13, 16, and 17), which all showed extensive centrilobular

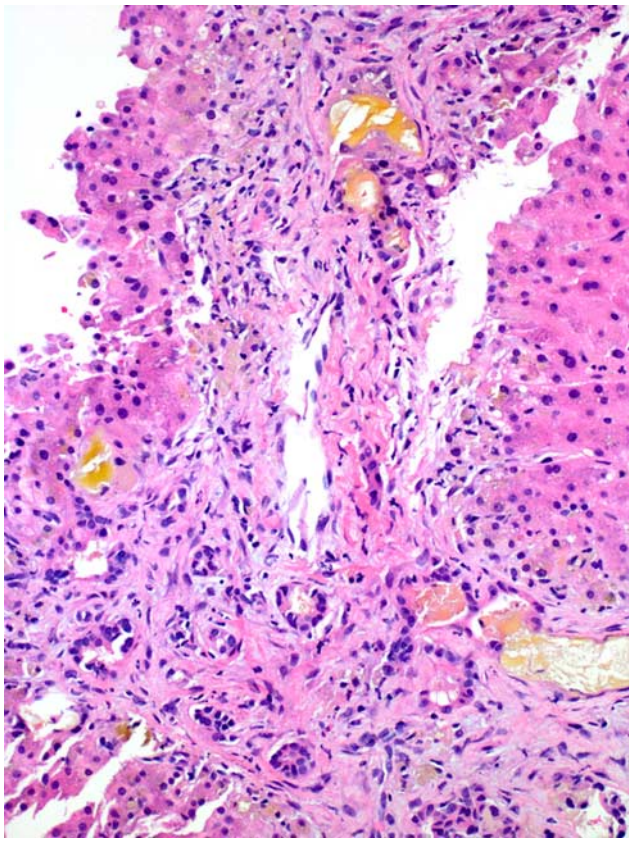

FIGURE 2. A case of cholangitis lenta showing mild portal fibrosis and ductular reaction. Portal edema is not evident.

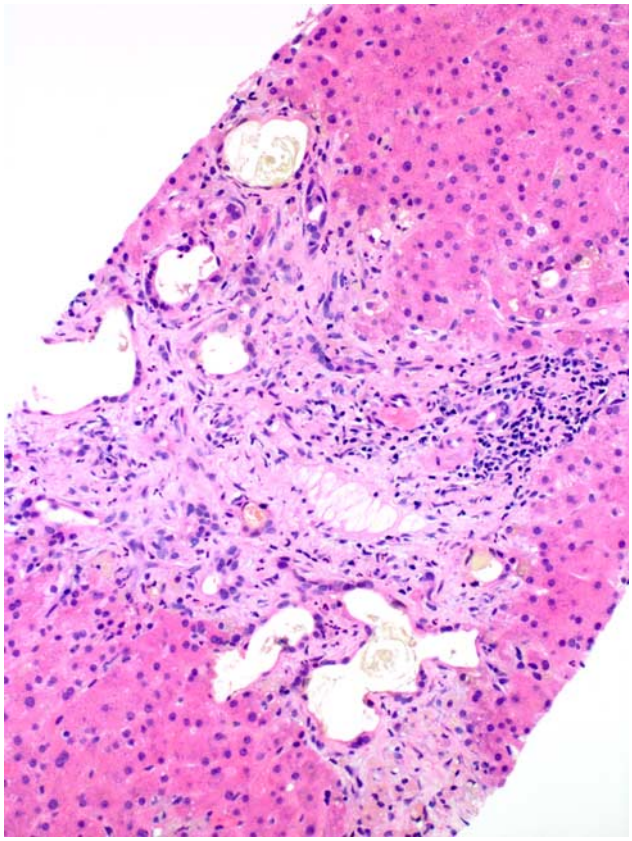

FIGURE 3. A case of cholangitis lenta showing mild inflammatory cell infiltrates in a portal tract, consisting mainly of lymphocytes and neutrophils. Mild portal fibrosis is noted. Portal edema is not evident.

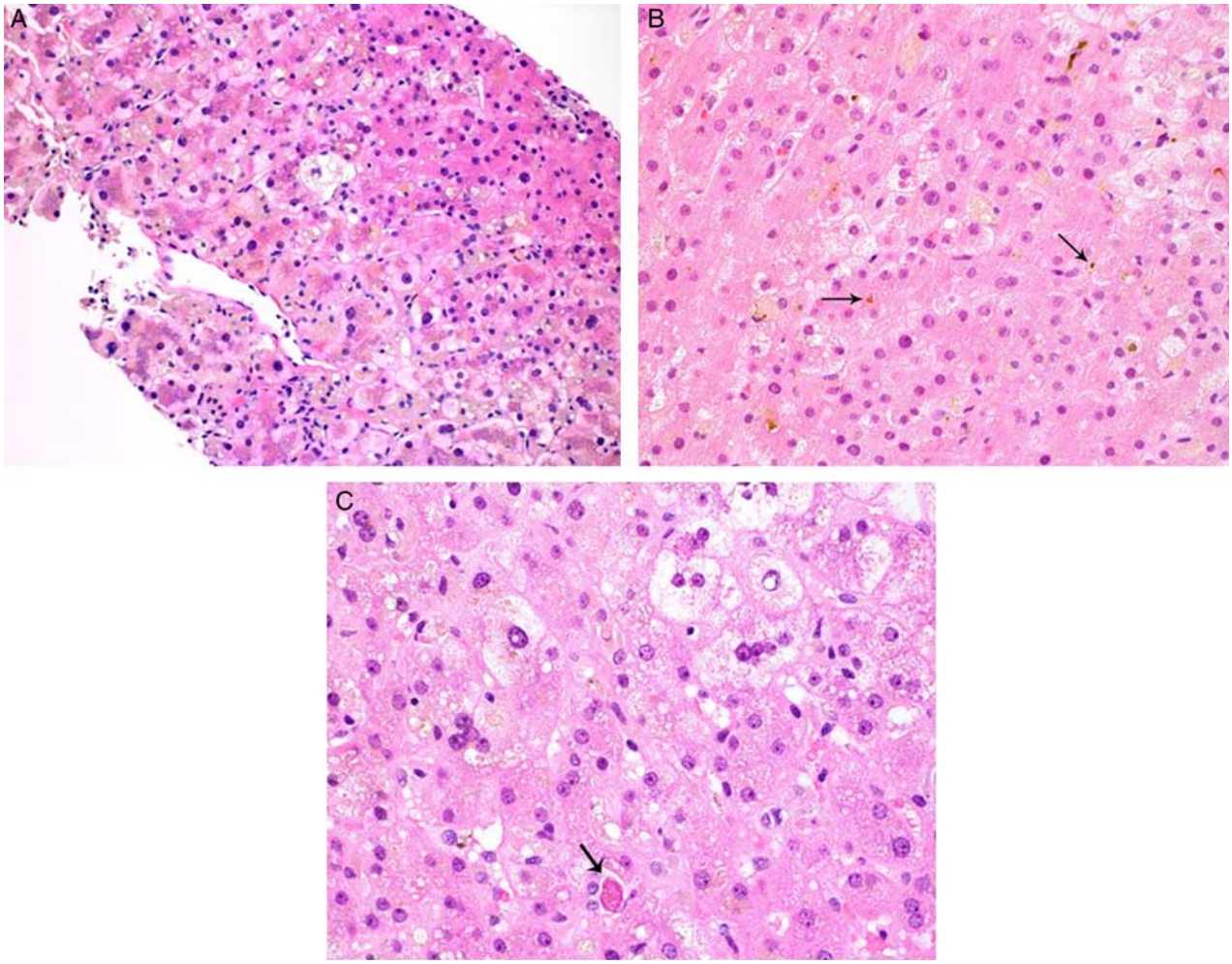

FIGURE 4. A case of cholangitis lenta showing features of lobular injury characterized by zone 3 pallor (A), prominent canalicular cholestasis (arrows; B), and the presence of ballooning hepatocytes and rare apoptotic hepatocytes (arrow; C).

necrosis with relative preservation of viable hepatocytes at zone 1 and preserved portal areas. The findings were consistent with "shock liver" because of ischemic injury, which was distinguished from postmortem autolysis where uniform disintegration of the hepatic architecture and hepatocyte morphology would be expected.

As shown in Table 4, 15 (53.6%) patients died during the course of their hospitalization, ranging from 2 days to 5 months after initial liver biopsy (mean, 56.6 d; median, 60 d). In comparison with those who survived the hospitalization, the patients who died showed higher serum aminotransferase levels, but their initial liver biopsies did not appear to show more significant hepatocyte injury. Among the 13 discharged patients (including 2 retransplanted patients), 4 (4/28; 14.3%) died during subsequent follow-up. Two patients (cases 22 and 24) died of pneumonia 7 and 11 months after initial liver biopsy, respectively. The other 2 (cases 3 and 21) died of graft dysfunction and fungal infection 9.3 and 3.6 years later, respectively. The remaining 9 (32.1%) patients were alive at the last follow-up, with the follow-up time ranging from 3.8 to 10.4 years (mean, 5.4 y; median, 5.3 y). Only 5 (5/28; 17.9%) of these patients recovered with good graft function, however. The remaining 4 (4/28; 14.3%) patients continued to suffer from graft dysfunction secondary to recurrent hepatitis C or multiple episodes of T cell-mediated rejection.

DISCUSSION

In this study, we have examined the largest series of liver biopsies showing characteristic histopathologic features of cholangitis lenta, correlated the biopsy findings with clinical and laboratory data, and detailed the patient outcome to investigate the role of the histopathologic diagnosis of cholangitis lenta in the clinical management of these patients. Our data show a high frequency (96.4%) of the signs and symptoms of sepsis in patients diagnosed with cholangitis lenta on liver biopsy, with 85.7% having had a clinically confirmed diagnosis. Our data also show that the patients with cholangitis lenta generally have a very poor prognosis with a high mortality rate, with more than half of our patients ultimately dying during the course of their hospitalization. These observations support

TABLE 4. Clinical Outcome and Follow-up in Patients With Cholangitis Lenta

Case	Main Findings on Follow-up Biopsy or Explant	Days From Initial Biopsy	Liver Transplantation	Days From Transplant Until Cholangitis Lenta on Biopsy	Redo Transplant	Clinical Outcome	Findings on Autopsy
1	No subsequent biopsy	NA	Y	16	N	Died (2 d after biopsy)	ND
2	No subsequent biopsy	NA	Y	11	N	Died (12 d after biopsy)	ND
3	Explant showing multifocal necrosis, hepatocyte ballooning, canalicular cholestasis, and persistent features of cholangitis lenta	18	Y	14	Y	Discharged home. Died of graft dysfunction because of worsening rejection 9 y and 3 mo later (multivisceral transplant recipient)	ND
4	No subsequent biopsy	NA	Y	18	N	Died (20 d after biopsy)	ND
5	Explant showing hepatocyte ballooning and persistent features of cholangitis lenta	26	Y	19	Y	Discharged home. Alive with recurrent HCV for 5 y and 8 mo at last f/u	NA
6	No subsequent biopsy	NA	Y	27	N	Died (2 mo after biopsy)	ND
7	Biopsy showing persistent features of cholangitis lenta	6	Y	10	N	Discharged home. Alive with recurrent HCV for 5 y and 5 mo at last f/u	NA
8	Biopsy showing persistent features of cholangitis lenta	15	Y	36	N	Discharged home. Alive with good graft function for 10 y and 5 mo at last f/u	NA
9	Biopsy showing mild portal and lobular inflammation and frequent apoptotic hepatocytes. Features of cholangitis lenta were not evident	60	Y	37	N	Died (3 mo after biopsy)	ND
10	No subsequent biopsy	NA	N	NA	NA	Died (2 mo after biopsy)	ND
11	Biopsy showing persistent features of cholangitis lenta with more pronounced cholestasis and hepatocyte ballooning	39	Y	25	N	Died (2 mo after biopsy)	ND
12	Biopsy showing persistent features of cholangitis lenta	17	Y	20	N	Discharged home. Alive with good graft function for 4 y and 4 mo at last f/u	NA
13	No subsequent biopsy	NA	Y	18	N	Died (5 d after biopsy)	Extensive necrosis consistent with shock liver
14	No subsequent biopsy	NA	Y	134	N	Died (4 mo after biopsy)	ND
15	No subsequent biopsy	NA	N	NA	NA	Discharged home. Alive with good graft function for 5 y and 11 mo at last f/u	NA
16	Biopsy showing persistent features of cholangitis lenta and foci of hepatocyte necrosis	42	Y	12	N	Died (2 mo after biopsy)	Extensive necrosis consistent with shock liver
17	Biopsy showing foci of necrosis. Features of cholangitis lenta were not evident	157	Y	42	N	Died (5 mo after biopsy)	Extensive necrosis consistent with shock liver
18	Biopsy showing persistent features of cholangitis lenta with more pronounced cholestasis	35	Y	43	N	Died (2 mo after biopsy)	ND
19	Biopsy showing minimized features of cholangitis lenta	19	Y	18	N	Discharged home. Alive with multiple episodes of ACR for 5 y and 4 mo at last f/u	NA
20	Biopsy showing persistent features of cholangitis lenta with more pronounced centrilobular injury	15	Y	23	N	Died (1 mo after biopsy)	ND
21	Biopsy showing minimized features of cholangitis lenta	44	Y	28	N	Discharged home. Died of respiratory failure because of fungal infection 3 y and 7 mo later	ND

TABLE 4. (*continued*)

Case	Main Findings on Follow-up Biopsy or Explant	Days From Initial Biopsy	Liver Transplantation	Days From Transplant Until Cholangitis Lenta on Biopsy	Redo Transplant	Clinical Outcome	Findings on Autopsy
22	Biopsy showing minimized features of cholangitis lenta, but zone 3 injury, lobular cholestasis and ductopenia were noted	73	Y	374	N	Discharged home. Died of pneumonia 7 mo later	ND
23	No subsequent biopsy	NA	N	NA	NA	Died (1 mo after biopsy)	ND
24	No subsequent biopsy	NA	Y	24	N	Discharged home. Died of pneumonia 11 mo later	ND
25	Biopsy showing persistent features of cholangitis lenta with foci of hepatocyte necrosis	120	Y	60	N	Died (3 mo after biopsy)	ND
26	Biopsy showing somewhat worsening features of cholangitis lenta	14	Y	18	N	Discharged home. Alive with multiple episodes of ACR for 3 y and 11 mo at last f/u	NA
27	No subsequent biopsy	NA	Y	22	N	Discharged home. Alive with good graft function for 3 y and 9 mo at last f/u	NA
28	No subsequent biopsy	NA	Y	30	N	Discharged home. Alive with good graft function for 3 y and 10 mo at last f/u	NA

ACR indicates acute cellular (T cell-mediated) rejection; f/u, follow-up; HCV, hepatitis C virus; N, no; NA, not applicable; ND, not done; Y, yes.

the notion that patients with a diagnosis of cholangitis lenta on liver biopsy require a full clinical work-up for underlying infectious processes and need immediate clinical attention for management.

Sepsis is a common clinical condition, with infection-related deaths being a leading cause of morbidity and mortality in the United States, as well as abroad.[9,10] Hepatic dysfunction is a common manifestation of sepsis, ranging from mild elevations of liver function tests to more severe findings such as jaundice or acute liver failure. Several studies have investigated the correlation of sepsis with hepatobiliary dysfunction in different epidemiologic groups. For example, hepatobiliary dysfunction has been found to be a common finding in the setting of sepsis in both neonatal[11,12] and adult patients.[3,13] The effects of sepsis on hepatic dysfunction are multifactorial, which may include the effects of bacterial toxins, hepatic hypoperfusion, the release of cytokines that induce acute-phase proteins, or by infection of the liver itself. In the current study, all patients showed abnormal liver function tests. Thus, liver function tests may serve as clinical indicators of hepatic involvement in patients with sepsis.

Cholestasis is commonly found in septic patients, which may include canalicular cholestasis, cytoplasmic cholestasis in hepatocytes, and ductular cholestasis.[14] Three histopathologic patterns have been described in this setting: (1) perivenular canalicular cholestasis with mild steatosis, prominence of Kupffer cells, and portal inflammation; (2) ductular cholestasis with inflammation; and (3) nonbacterial cholangitis associated with toxic shock syndrome.[2,15,16] Apparently, ductular cholestasis (cholangitis lenta) is a characteristic and unique feature of liver involvement in the setting of sepsis as confirmed by our study.

Despite the advance in antimicrobial prophylaxis, postoperative infection remains as a relatively common complication of liver transplantation. Bacteremia has been shown to have a major impact on the morbidity and mortality of liver transplant patients.[17–21] The most common primary site of infection in the setting of liver transplantation is the abdomen, with 1 study showing 30% of infections occurring at this site.[20] Other common sites of infection include the blood stream, respiratory tract, surgical site, and urinary tract. Many factors predispose liver transplantation patients to bacterial colonization of the biliary tree. These include the immunosuppressed state, altered biliary motility leading to decreased clearance of ascending bacteria, the use of plastic biliary stents in the surgical procedure, and stricture formation.[5] The results of our study further emphasize the critical role infection plays in the morbidity and mortality of liver transplantation patients. Indeed, 25 of 28 patients with cholangitis lenta in our study were liver transplant recipients, with the majority having had transplantation performed within 1 month.

There have been only a few studies to date that have suggested an association of cholangitis lenta with bacterial and fungal infection.[2–5] The small case series by Lefkowitch[2] published in 1982 was the first study that investigated the clinical significance of cholangitis lenta. It was through the postmortem examination of 3 cases that the belief began to shift away from mechanical obstruction of bile ducts as the underlying mechanism of these findings to severe infection that led to sepsis and functional alteration of bile flow. In the study by Lin et al,[5] all 9 pediatric liver transplant recipients who showed histopathologic features of cholangitis lenta on their posttransplant

biopsies had proven bacterial or fungal infection related to cholestasis. Only 2 patients had concurrent biliary obstruction. Our data corroborate these observations and further establish a strong association of cholangitis lenta with infection and sepsis. No cases were found to be associated with biliary obstruction in our study.

The exact pathophysiologic mechanisms of cholangitis lenta remains unclear. Lefkowitch and others have hypothesized that bacterial endotoxin release and subsequent damage may cause ductular proliferation and impaired bile flow. Slowed bile flow in tortuous ductules leads to enhanced water reabsorption, causing a "dehydration" effect to form bile concrement. Increased permeability of canalicular tight junctions may also cause water escape from bile, which could contribute to canalicular cholestasis. In addition, ductular cholestasis may lead to localized secondary obstruction, which may further aggravate ductular proliferation and cholestasis.[2,5,22–26]

Our study also confirms previous observations that cholangitis lenta is associated with a poor prognosis. In the study by Lefkowitch,[2] all 3 patients died. In the study by Lin et al,[5] only 3 (33%) patients recovered with normalized graft function. Two patients required retransplantation for graft failure within a few weeks after the diagnosis of cholangitis lenta. The remaining 4 patients had only partial recovery of graft function, and all died months or years later after the diagnosis.[5] In our series, 53.6% of patients died within 5 months after diagnosis during their initial hospitalization. Two patients received retransplantation within 1 month. Only 5 (17.9%) survived patients maintained good graft function.

In addition to the diagnostic hallmark of cholangitis lenta, we observed a wide spectrum of histopathologic features in liver biopsies. These include varying degrees of bile duct injury, canalicular cholestasis, hepatocyte ballooning, hepatocyte necrosis/apoptosis, steatosis, and zone 3 damage. Although preservation injury may contribute to some extent given the timing of most posttransplant graft biopsies, the presence of similar findings in grafts biopsied months after transplantation (such as case 14) suggests that they likely represent part of the histologic spectrum of liver injury associated with cholangitis lenta. Minimal to mild portal inflammation with lymphocytes and neutrophils is a consistent finding in the setting of cholangitis lenta. This may cause confusion with biliary obstruction, particularly in the presence of portal and periportal fibrosis. However, portal edema, which is a common feature of biliary obstruction, is uncommon in biopsies showing cholangitis lenta. The characteristic ductular dilatation with inspissated bile should help distinguish from biliary obstruction. Interestingly, features of nodular regenerative hyperplasia were observed in grafts as early as 10 days posttransplantation in our series. The underlying pathogenesis is unclear but multifactorial mechanisms are suspected, which may include regenerative changes in response to hepatocyte injury, medication effects (such as those by immunosuppressive agents), and hemodynamic alterations at the level of microvasculature in grafts.[27,28]

In conclusion, the histopathologic diagnosis of cholangitis lenta on a liver biopsy signals that the patient may have a serious underlying local or systemic infection. It portends a poor clinical prognosis in general, particularly in the liver transplant setting. It is thus critical that patients with this diagnosis should receive a thorough work-up for infectious etiologies and aggressive medical management.

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