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Original contribution

Follicular cholecystitis: clinicopathologic associations☆,☆☆

Behzad Salari MD, Neda Rezaee MD, Angus Toland MS, Deyali Chatterjee MD*

Department of Pathology and Immunology, School of Medicine, Washington University in St. Louis, St. Louis, MO, USA 63110

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Summary Follicular cholecystitis (FC) is a relatively rare entity with uncertain causal associations. In this study, we aimed to explore different clinicopathologic associations of FC, and to better characterize the entity. A retrospective review of archival hematoxylin and eosin slides and pertinent clinical information was undertaken for all cholecystectomy cases with a rendered diagnosis of "follicular cholecystitis," from 1991 to 2017. Concurrent conventional chronic cholecystitis (CC) and lymphocytic cholecystitis (LC) were documented. Forty-three consecutive patients were confirmed to have FC. The majority of the patients (88.4%) had at least one other histologic association in the gallbladder (LC, CC, or both). Remarkably, functional distal biliary obstruction (from choledocholithiasis, sclerosing cholangitis, distal biliary strictures, or malignancies of the pancreatic head or ampulla) was found in 76.7% of the patients, irrespective of the presence of other concurrent histologic findings. FC associated with CC was relatively more common in females (61%) and strongly associated with cholelithiasis (70%). However, those without CC were predominantly males (70%) and had a significant association with LC (75%). All four cases of FC without any other histologic associations who had clinical information available showed some form of distal biliary obstruction. FC cases without concurrent LC were often associated with CC (74%). FC is strongly associated with extrahepatic biliary obstruction distal to the gallbladder. Therefore, this finding at routine cholecystectomy may warrant further evaluation to rule out a cause for distal biliary tract obstruction. Additionally, it is commonly associated with other concomitant histologic abnormalities in the gallbladder such as CC and/or LC.

1. Introduction

Chronic cholecystitis is the most frequent pathologic diagnosis in cholecystectomy specimens. It is characterized by the microscopic appearance of chronic inflammatory cells, including scattered lymphocytes, macrophages, plasma cells, and eosinophils, occasionally associated with a few neutrophils. The wall of the gallbladder is thickened and Rokitansky-Aschoff sinuses are often numerous and prominent in cases of chronic cholecystitis. Lymphoid follicles

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* Corresponding author at: Department of Pathology and Immunology, Washington University in St. Louis, 425 S Euclid Ave, Campus Box 8118, St. Louis, MO, USA.

E-mail address: deyali@wustl.edu (D. Chatterjee).

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may be present as part of the chronic inflammation. However, rarely, lymphoid follicles may be the prominent histologic feature in a cholecystectomy specimen—a condition then called follicular cholecystitis (FC). Some authors have assigned a random cut-off to give objectivity to the diagnostic criteria, such as follicles reaching a density of three per centimeter [1]. The follicles can be found anywhere in the wall of the gallbladder, but predominantly involves the mucosa. This lesion was previously labeled "pseudolymphoma of the gallbladder" and has also been referred to lymphoid hyperplasia of the gallbladder.

FC is a relatively rare entity, and little is known about the etiopathology of the condition. Causal associations reported infrequently in the literature have mainly included gram-negative bacterial infection [1-5]. In this study, we aimed to better characterize this entity, and to investigate whether this reaction pattern has any clinical significance of its own or is just a variant of chronic cholecystitis.

2. Materials and methods

With approval from the institutional review board (IRB), a retrospective study was conducted on all cholecystectomy cases with a rendered diagnosis of "follicular cholecystitis," between January 1991 and August 2017, at Barnes Jewish Hospital. All archival hematoxylin and eosin (H&E) slides and pertinent clinical information from the medical records, including laboratory data and imaging findings, were reviewed. Functional distal biliary obstruction was considered in the setting of evidence confirmed by imaging studies or from a pathologic diagnosis that impeded bile flow significantly enough to give rise to abnormal liver function tests manifested by elevated bilirubin, alkaline phosphatase, or γ-glutamyl transferase. In particular, such conditions included large stone impacted in the cystic duct, choledocholithiasis, primary or secondary sclerosing cholangitis, distal biliary strictures by other benign conditions or by

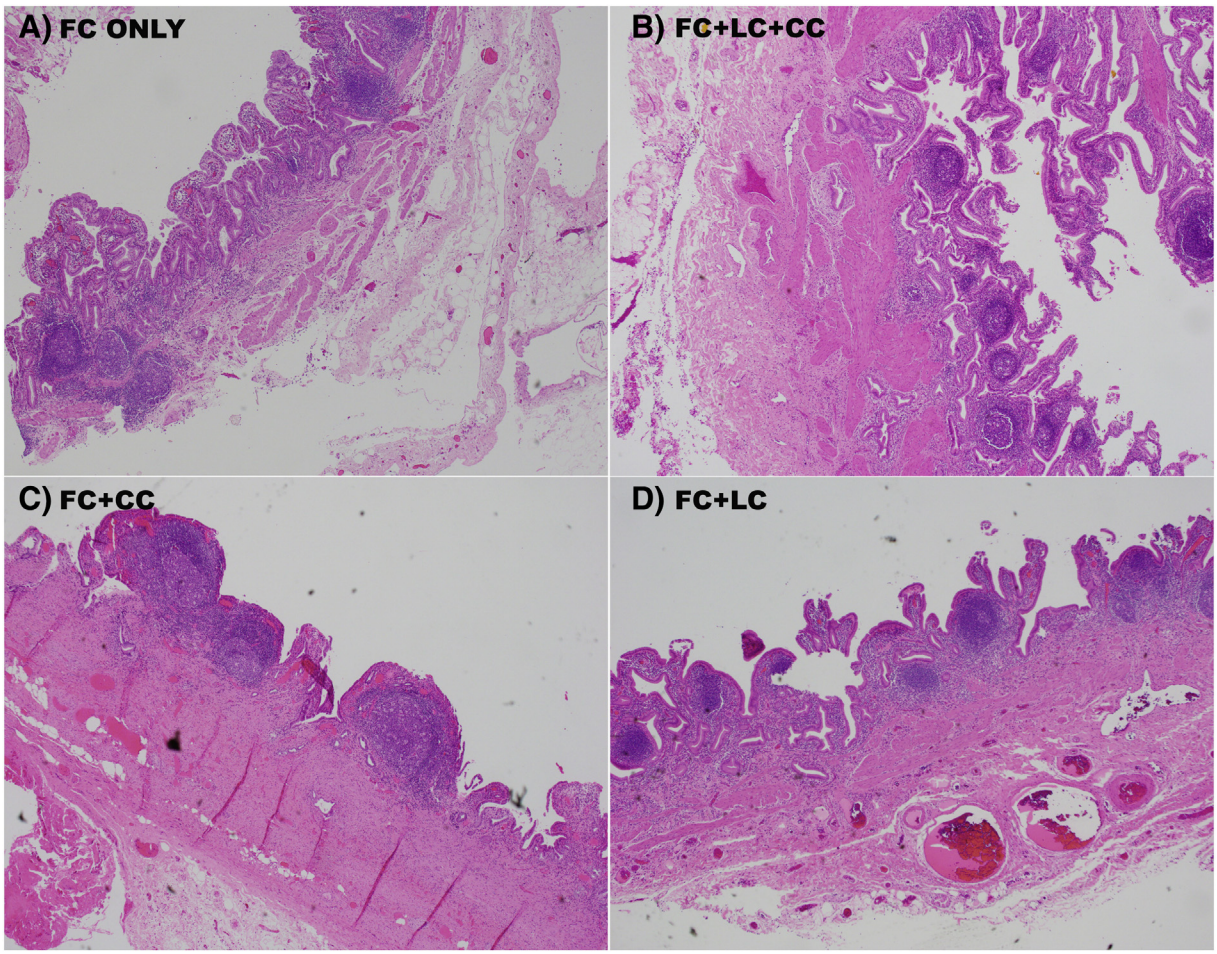

Figure H&E sections, original magnification ×20. A, FC with the presence of more than occasional reactive lymphoid follicles, distributed anywhere in the gallbladder wall. B, Concomitant histologic abnormalities including conventional CC, and LC. C, Concomitant FC (presence of reactive lymphoid follicles) and CC (fibromuscular hyperplasia of the gallbladder wall along with Rokitansky-Aschoff sinuses). D, Concurrent FC and LC (with diffuse band-like mucosal infiltrate of lymphocytes).

malignancy, including a neoplasm in the pancreatic head or ampulla.

2.1. Diagnostic criteria of follicular cholecystitis

Most cases diagnosed with follicular cholecystitis had prominent lymphoid aggregates as the predominant histologic feature in those cholecystectomies. Our inclusion criteria for this study included the presence of more than occasional reactive lymphoid follicles, distributed anywhere in the gallbladder wall (Figure A). Since this is a retrospective study with archival slides, which were sampled without a strict standardized grossing protocol, an objective diagnostic criterion was not framed. Each case was reviewed to confirm the diagnosis of FC, and to note other histologic features including concurrent conventional chronic cholecystitis (CC) or lymphocytic cholecystitis (LC). CC was determined by the presence of fibromuscular hyperplasia of the gallbladder wall along with the presence of Rokitansky-Aschoff sinuses (Figure B and C). Concurrent LC was noted based on the presence of diffuse mucosal infiltrate of lymphocytes (Figure B and D).

2.2. Data analysis

Each patient's data was inserted into an Excel database (Microsoft, Redmond, WA, USA), and evaluated by descriptive statistical analysis. The results for each variable were expressed in frequency, percentage, and median or mean value ± standard deviation (SD).

3. Results

During a 26.5-year period (January 1991 to August 2017), a total of 19 262 cholecystectomies were performed at our institution. Forty-three consecutive patients were confirmed to have FC (0.2%). The median age was 67 years (range, 31-95 years). Of these patients, 53.5% were male and 46.5% were female. The majority of the patients were Caucasian (72.3%), followed by African-Americans (23.4%) and one patient was Asian (2.1%). Concurrent histological findings included CC (32.6%), LC (34.9%), or both (20.9%). Table 1 summarizes the demographic profile and significant clinicopathologic findings.

Functional distal biliary obstruction was found in 76.7% of the patients, irrespective of the presence of other concurrent histologic findings (Table 2). Thirty-eight patients with FC (88.4%) had at least one other histologic association in the gallbladder (LC, CC, or both). FC associated with CC was relatively more common in females (61%) and strongly associated with cholelithiasis (70%). In contrast, FC associated with LC was relatively more common in males (63%) and associated with cholelithiasis only in 46% of the patients. A majority (67%) of the cases which did not have an association with CC had some form of distal obstruction. Moreover, FC

Table 1 Demographics and clinicopathologic association of follicular cholecystitis

Histological findings	Age (median, years)	Gender (% males)	Race (% African-American)	Functional distal biliary obstruction (%)	Association with gallstones (%)	Other histologic association
All FC (n = 43, 100%)	67	53.5	23	76.7	53.5	
FC + CC (n = 23, 53.5%)	67	39	17	83	70	39% with LC
FC-CC (n = 20, 46.5%)	68	70	32	70	35	75% with LC
FC + LC (n = 24, 55.8%)	70	63	21	75	46	38% with CC
FC-LC (n = 19, 44.2%)	66	42	26	79	63	74% with CC
FC + LC + CC (n = 9, 20.9%)	74	56	0	89	67	1 case with actinomycetes infection of gallbladder
FC + CC-LC (n = 14, 32.6%)	63.5	29	29	79	71	
FC + LC-CC (n = 15, 34.9%)	62	67	33	67	33	
FC alone (n = 5, 11.6%)	71	80	20	100[a]	40	

Abbreviations: FC, follicular cholecystitis; CC, conventional chronic cholecystitis; LC, lymphocytic cholecystitis.
[a] Missing clinical record in 1 patient.

Table 2 Frequency of distal biliary obstruction in follicular cholecystitis

Histological findings	Any extra-hepatic biliary stone	Cholelithiasis	Choledocholithiasis	Neoplasia in the pancreatic head or ampulla	PSC	Other findings
All FC (n = 43, 100%)	28 (65.1%)	23 (53.5%)	11 (25.6%)	7	2	CDF (n = 1) BS (n = 1) ChC (n = 1) GBC (n = 1)
FC + CC (n = 23, 53.5%)	18 (78.3%)	16 (69.6%)	6 (26.1%)	2	1	CDF (n = 1) BS (n = 1) GBC (n = 1)
FC-CC (n = 20, 46.5%)	10 (50.0%)	7 (35.0%)	5 (25.0%)	5	1	ChC (n = 1)
FC + LC (n = 24, 55.8%)	13 (54.2%)	11 (45.8%)	6 (25.0%)	5	2	GBC (n = 1)
FC-LC (n = 19, 44.2%)	15 (78.9%)	12 (63.2%)	5 (26.3%)	2	0	CDF (n = 1) BS (n = 1) ChC (n = 1)
FC + LC + CC (n = 9, 20.9%)	7 (77.8%)	6 (66.7%)	3 (33.3%)	1	1	GBC (n = 1)
FC + CC-LC (n = 14, 32.6%)	11 (78.6%)	10 (71.4%)	3 (21.4%)	1	0	CDF (n = 1) BS (n = 1)
FC + LC-CC (n = 15, 34.9%)	6 (40%)	5 (33.3%)	3 (20.0%)	4	1	
FC alone [a] (n = 5, 11.6%)	4 (80.0%)	2 (40.0%)	2 (40.0%)	1	0	ChC (n = 1)

Abbreviations: PSC, primary sclerosing cholangitis; FC, follicular cholecystitis; CC, conventional chronic cholecystitis; LC, lymphocytic cholecystitis; CDF, cholecysto-duodenal fistula; BS, biliary stricture; ChC, cholangiocarcinoma; GBC, gallbladder carcinoma.

[a] Missing clinical record in 1 patient.

cases without concurrent LC were often associated with CC (74%). All four cases of FC without any other histologic associations who had clinical information available, showed some form of distal biliary obstruction.

3.1. Follow-up

Patients were followed up for a median duration of 5 years (range, 1.1-15.9) and the following events were observed: one patient had recurrent choledocholithiasis requiring stent placement; one patient had relapsed diffuse large B-cell lymphoma—he had prior history of diffuse large B-cell lymphoma with a large mass in his retroperitoneum as well as metastatic lesions in his brain, and had been initially diagnosed before cholecystectomy; one patient was diagnosed with hepatocellular carcinoma with omental, peritoneal, and pleural metastasis; one patient experienced recurrence of primary sclerosing cholangitis (PSC); and one patient had recurrent pancreatitis.

4. Discussion

A recent case series of over 2400 patients [6] demonstrated FC to be present in less than 2% of all chronic cholecystitis specimens. In our study population, the incidence was noted to be 0.2%. The even lower incidence in our study could be due to selection error as we searched for cases which were called FC in the diagnostic report, and it is possible that some true cases of FC were simply called CC in the diagnostic line and was not captured in our study cohort. The previous study found the lesion to be present in older patients, with a mean age of 65 years versus 49 years in non-FC patients [6]. This matches our study population (median age, 67 years), and in both studies, this entity is observed to occur in an older population than is described typically for chronic cholecystitis.

As it has been reported in other tissues, lymphoid hyperplasia is often a reactive process concurrent with chronic inflammatory conditions, such as rheumatologic disease or infection [7]. Although a reactive process, the same logic does not apply to FC developing on a long-standing CC. Our study suggests that it probably has a different etiopathogenesis than CC. Historically, FC has been associated with gram-negative bacterial infections, including *Escherichia coli*, *Klebsiella pneumoniae*, and *Salmonella typhi* [1-3]. Moreover, many patients with CC have detectable *Helicobacter pylori* infection of the gallbladder mucosa, especially those with pyloric metaplasia, though this does not appear to predict the specific histologic subtype [8]. These associations with various infectious agents may suggest a reactive etiology for some cases of cholecystitis, which can give rise to FC. For our retrospective study, the limitation in this regard was unavailability of patient data on the results of bile culture, unless it was specifically performed to answer a clinical question (in recent years, it is no longer performed as a routine work up for biliary tract diseases, including cases suspected for cholecystitis). Therefore, this finding could not be corroborated in our study population. Of note, one case in our cohort did show morphologic evidence of actinomycetes within the gallbladder with FC. For other cases, however, our follow-up data shows that none of these incidentally diagnosed FC cases underwent any procedure to detect infection in the biliary system or received any antibiotics after cholecystectomy. Though the entity is rare and benign, it is important to distinguish this form of cholecystitis from lymphomas arising in the gallbladder, such as MALT lymphoma and follicular lymphoma as the histologic appearances can be similar [9,10]. In our experience, all cases of FC had lymphoid follicles with secondary germinal centers, which helped distinguish this reactive process from neoplastic processes by H&E morphology alone.

Our study of 43 cases of FC demonstrated that most cases (88.4%) had a co-occurring histology of CC and/or LC. Most patients (76.7%) had an identifiable distal obstruction in the bile duct due to cholelithiasis, choledocholithiasis, sclerosing cholangitis, or a neoplasm in the pancreatic head or ampulla.

A study of patients with a variety of distal biliary obstructive disease and cholecystectomy to evaluate the histopathology of those gallbladders has been reported in the literature [11]. This study demonstrated that 70% (14/20) gallbladders in the PSC cohort, 60% (3/5) gallbladders in the choledocholithiasis cohort, and 60% (12/20) of gallbladders with obstructive adenocarcinoma of the pancreas head, ampulla of Vater, or duodenum demonstrated “mucosal or deep lymphoid nodules.” These gallbladders also had intense diffuse lymphoid infiltrates, mucosal active inflammation (neutrophilic), and foci of metaplasia (gastric or intestinal), though the latter was more common in PSC (85%) than in malignancy-associated gallbladders (35%). This histology was, however, not a statistically-significant pattern in these gallbladders. In addition, it is unclear whether the sections evaluated met the criteria for FC.

In a previous study by the same group, the gallbladder histology in patients with lymphoplasmacytic sclerosing pancreatitis (LPSP), a form of chronic pancreatitis with pancreatic duct fibrosis and in the current context likely termed as autoimmune pancreatitis, a similar histologic appearance of diffuse lymphocytic infiltrate and lymphoid nodules was observed in 60% (12/20) of gallbladders [12]. However, only 13 (65%) of LPSP patients had common bile duct strictures or intrapancreatic bile duct inflammation with no correlation between obstruction and lymphoid follicles. Interestingly, many cases of LPSP are associated with inflammatory bowel disease (IBD) and autoimmune diseases (Sj gren's syndrome) [13].

Another study evaluating the histology of CC in patients with IBD reported “nodular lymphoid aggregates” to be present more frequently in Crohn's disease patients with acalculous cholecystitis (21.2%) compared to non-IBD controls (5%) [14]. Based on the authors' histologic criteria (lymphoid

aggregates in the mucosa, smooth muscle, and/or full thickness), some (or all) of these cases may represent follicular cholecystitis as well. Because IBD is often associated with PSC and LPSP [15], it would be interesting to further characterize the association between IBD and FC. Taken together, these studies may suggest chronic biliary obstruction as a cause for the FC pattern on gallbladder histology.

In our study, cases of FC without any other histologic associations showed some form of distal biliary obstruction. Although this number is small, this association seems significant. FC associated with CC was relatively more common in females (61%), as well as being strongly associated with cholelithiasis (70%). The demographic profile and etiologic association reflect calculous cholecystitis. It is likely that the development of FC in this background is related to superimposed biliary tract obstruction by gallstones, either obstructing the cystic duct or bile duct. Again, FC associated with LC was relatively more common in males (63%) and associated with cholelithiasis only in 46% of the patients. Cases of LC in our study group, which did not have CC, had a 67% association with functional distal obstruction, which in fact showed a lower association from FC with CC only, without LC (89%).

LC is a histologic entity on the differential when considering a diagnosis of FC. LC is defined by the presence of a subepithelial band-like, dense infiltrate of lymphocytes while lymphoid follicles are characteristically absent [4]. The clinical significance of this distinction is not clear, since etiologically both are related to distal biliary obstruction. However, FC may result from superimposed bacterial infections, an association that has been suggested in previous studies. Additional studies will likely better elucidate the differences (or lack thereof) between the two entities. However, as mentioned above, there was significant overlap between these two entities in our cohort.

5. Conclusions

FC is commonly associated with other concomitant histologic abnormalities in the gallbladder such as CC and/or LC. Additionally, it is strongly associated with extrahepatic biliary obstruction distal to the gallbladder. Therefore, this finding at routine cholecystectomy may warrant further evaluation to rule out a cause for distal biliary tract obstruction, if such a cause is not already established. This is the first study that supports the etiologic association of distal biliary obstruction to FC. Prospective studies will be needed to better establish the association of FC with distal biliary obstruction, since retrospective studies such as ours may have the limitation of under-reporting this diagnosis.

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