Lymphocytic Cholecystitis/Cholangitis

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ABSTRACT

Objectives: To describe four cases of an uncommon type of acalculous cholecystitis/cholangitis characterized by increased intraepithelial lymphocytes within the biliary epithelium.

Methods: Cases were prospectively compiled during regular surgical pathology sign-out. Clinical information was obtained from the electronic medical record and the gross appearance from the surgical pathology reports. Microscopic examination was performed with emphasis on the type, location, and distribution of the inflammatory pattern; presence of intraepithelial lymphocytes (>30 per 100 biliary cells); and presence of metaplasia and epithelial hyperplasia. Immunohistochemical stains for CD3, CD8, and IgG4 were performed in some cases.

Results: All patients were adults who had either biliary pain or obstructive symptoms. All gallbladders had a relatively normalgross appearance and did not contain gallstones or biliary sludge. Microscopic examination showed numerous intraepithelial lymphocytes in the biliary epithelium. The mucosa was frequently expanded by dense inflammatory cell infiltrates. The inflammatory process was more severe in the infundibulum and bile ducts than in the body of the gallbladder. The intraepithelial lymphocytes were CD3+, CD8+, and IgG4+ plasma cells were absent.

Conclusions: The term lymphocytic cholecystitis/cholangitis is proposed. The potential clinical implications and pathogenesis of this inflammatory pattern and the differential diagnosis with other forms of acalculous cholecystitis are discussed.
Materials and Methods

Over the course of 21 years, four cases of lymphocytic cholecystitis/cholangitis were prospectively identified by the author during regular surgical pathology sign-out, three at the University of Minnesota and one at New York Presbyterian Hospital, Weill Cornell Medical Center. The histopathologic diagnosis of lymphocytic cholecystitis/cholangitis was based on the presence of increased intraepithelial lymphocytes (>30 per 100 biliary cells) within the gallbladder mucosa/bile ducts. In addition, several histologic parameters were assessed in each case, including the type, location, and distribution (focal, patchy, or diffuse) of inflammatory cell infiltrates within the epithelium and lamina propria, the presence of pyloric or intestinal metaplasia, cholesterolosis, Rokitansky-Aschoff sinuses, thickening of the muscularis, fibrosis, and inflammatory involvement of biliary glands. Immunohistochemical stains for CD3, CD4, CD8, and CD20 were performed in three cases and IgG4 in two cases. The clinical information and the gross description of the cholecystectomy specimens, including the presence of gallstones, were retrospectively retrieved from the patients’ records and pathology reports, respectively.

Results

Clinical Information

The clinical information is summarized in Table 1. There were two men and two women with a median age of 64 years (range, 33-80 years). Three had epigastric pain. One patient had nausea and vomiting, as well as painless jaundice. Imaging studies suggested the presence of small gallstones, biliary sludge, adenomyosis, and distal bile duct narrowing concerning for tumor. Abnormal hepatic liver tests were present in two patients. Three patients underwent laparoscopic cholecystectomy, and in one, the gallbladder was included in a Whipple resection.

Pathologic Examination

Gross Appearance

All gallbladder specimens had a normal external appearance. Upon opening, there were no gallstones or biliary sludge. The mucosa was either normal or slightly congested. In two patients, there was mild thickening of the gallbladder wall.

Microscopic Examination

Sections of the infundibulum and cystic ducts as well as representative sections of the body were available in all cases.

The infundibulum, cystic duct, and distal common bile duct in the patient who underwent Whipple resection were more inflamed compared with the body of the gallbladder. At these sites, the mucosa was thickened due to expansion of the lamina propria by inflammatory cells consisting primarily of lymphocytes, histiocytes, and few plasma cells. Numerous intraepithelial lymphocytes (>30 per 100 biliary cells) were present throughout the mucosa. Neutrophilic infiltrates (active lesions) were absent in the lamina propria and within the epithelium.

A similar inflammatory pattern, albeit less dense, was present in sections from the body of the gallbladder. Intraepithelial lymphocytes had a diffuse (one case) or patchy (three cases) distribution.
were essentially confined to the mucosa with marginal involvement of the muscularis, with the exception of one case that showed Crohn-like lymphoid infiltrates. Pyloric metaplasia was present in two cases. No intestinal metaplasia, cholesterosis, or Rokitansky-Aschoff sinuses were observed. Two cases showed a hypertrophic muscularis. There was no vasculitis.

Most intraepithelial lymphocytes were CD3+ CD8+ T cells with few CD4+ cells. The latter cells were more abundant within the lamina propria. Few CD20+ B cells and no IgG4 staining plasma cells were present within the mucosa.

A large cell B-cell lymphoma was present in the peri-pancreatic lymph nodes of the patient who had the Whipple resection. This procedure was performed under the assumption that there was a malignant tumor obstructing the distal bile duct with lymph node metastases. However, there was no evidence of pancreatic carcinoma or common bile duct obstruction by lymphoma. The distal common bile duct showed lymphocytic cholangitis and a focal increase in these cells may be present within the gallbladder epithelium of patients with chronic calculous cholecystitis. However, it is never the predominant inflammatory pattern. In addition, we did not recognize certain inflammatory patterns may assist in the identification of the type of inflammatory biliary disease since some types of acalculous cholecystitis are associated with biliary disorders that differ in their pathogenesis and response to treatment.

This report describes a novel form of chronic acalculous cholecystitis characterized by an increased number of intraepithelial lymphocytes. When this inflammatory pattern occurs in the stomach, colon, esophagus, and duodenum, it has been called lymphocytic gastritis, colitis, esophagitis, and duodenal lymphocytosis, respectively. By analogy, the term lymphocytic cholecystitis/cholangitis was chosen for this condition.

Lymphocytic cholecystitis/cholangitis is an extremely rare disorder. The author has seen only four cases in more than 20 years of surgical pathology practice. As for most gallbladder disorders, the most common symptom was epigastric pain with clinical features of a biliary colic. Although imaging studies suggested the presence of sludge or stones in two patients, neither were found when the intact gallbladder was inspected. In fact, imaging studies might not be able to detect this condition since all gallbladders had a relatively normal gross appearance.

Few (three to four per 100 biliary cells) intraepithelial lymphocytes are commonly observed in normal gallbladder specimens excised from the donor’s liver and used for hepatic transplants. A focal increase in these cells may be present within the gallbladder epithelium of patients with chronic calculous cholecystitis. However, it is never the predominant inflammatory pattern. In addition, we did not...
Mucosal expansion may result in partial obstruction of bile flow, which might clinically manifest as biliary colic or, when located distally, jaundice. The presence of a hypertrophic muscularis in two patients is consistent with this interpretation. Although the inflammatory changes were mostly confined to the mucosa, deep biliary glands were also inflamed. This distribution is consistent with an inflammatory process that targets epithelial cells.

The pathogenesis of this entity is unknown. As in other organs of the gastrointestinal tract, the inflammatory pattern suggests an immune reaction to luminal antigens, which, in the case of the gallbladder and bile ducts, may be either bile constituents or drugs excreted through bile.
consideration is that this condition might be triggered by an immune-mediated disorder in a different organ of the gastrointestinal tract, as has been observed in some patients with celiac disease in whom biopsy specimens of the stomach and/or colon may show lymphocytic gastritis and colitis, respectively. This association is thought to result from homing of circulating activated lymphocytes throughout the gastrointestinal mucosa. However, when this mechanism is responsible for increased intraepithelial lymphocytes, there is usually no or minimal evidence of epithelial cell injury or hyperplasia. In this series, the duodenal mucosa in the patient who underwent Whipple resection did not show increased intraepithelial lymphocytes. No additional gastrointestinal biopsy specimens were available from the other patients.

It is possible that some patients with this condition have been diagnosed clinically as having biliary dyskinesia. This diagnosis is considered when patients have vague postprandial pain in the absence of cholelithiasis and is confirmed by an abnormal gallbladder ejection fraction on hepatobiliary iminodiacetic acid scan. More than half of the excised gallbladders have inflammatory changes. However, the pathologic findings in studies focusing on the pathology of biliary dyskinesia are simply described as acute or chronic cholecystitis without further elaboration on the characteristics of the inflammatory pattern.

The differential diagnosis of lymphocytic cholecystitis includes other types of chronic acalculous cholecystitis. Diffuse lymphoplasmacytic acalculous cholecystitis is characterized by a diffuse mucosis in which the lamina propria is infiltrated predominantly by lymphocytes and plasma cells. Active lesions (intraepithelial neutrophils) are occasionally present. Intraepithelial lymphocytes are not increased. This inflammatory pattern was initially thought to be specific for gallbladder involvement in patients with primary sclerosing cholangitis. However, it was subsequently demonstrated that the same pattern may be seen in obstructive cholecystitis. IgG4-related cholecystitis/cholangitis is another disorder that shows the same type of mucositis. Obliterative phlebitis, when present, may facilitate this diagnosis. This condition may affect exclusively the biliary tract or be associated with autoimmune pancreatitis. The differential diagnosis is established by the demonstration of an increased number of IgG4–secreting plasma cells (<15%) for IgG4. Plasmacytoid lymphocytes (<15%) are positive. The gallbladder also shows a similar inflammatory pattern that mimics closely follicular cholecystitis associated with gallstones. At variance with lymphocytic cholecystitis, there is no increase in intraepithelial lymphocytes. In addition, lymphoid follicles with reactive germinal centers are not observed in lymphocytic cholecystitis.

Other forms of chronic acalculous cholecystitis, such as eosinophilic or lymphoepitheliocytic cholecystitis, are easy to differentiate from lymphocytic cholecystitis based on the abundance of eosinophils. None of our cases was associated with a demonstrable infectious etiology. In addition, there is no mention of increased intraepithelial lymphocytes in publications of infectious acalculous cholecystitis.

In summary, there appears to be a form of chronic cholecystitis/cholangitis characterized by the presence of abundant intraepithelial lymphocytes. This condition affects predominantly the infundibulum of the gallbladder and bile ducts and may be associated with epithelial hyperplasia and outflow obstruction. As in other organs of the gastrointestinal tract, this inflammatory pattern suggests an immune-mediated reaction to luminal antigens, either intrinsic (bile constituents) or extrinsic (drugs), or homing to the biliary epithelium of circulating lymphocytes in patients with other conditions.

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References


