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Original Research Article

Chronic cholecystitis with follicular lymphoid hyperplasia: nomenclature and diagnostic dilemmas

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ABSTRACT

Background: To revisit the nomenclature, prevalence, histogenesis and the diagnostic dilemmas in cases of cholecystitis with lymphoid hyperplasia received in a private laboratory in one-year duration.
Methods: A total of 51 cases of cholecystectomy were examined histopathologically to identify and review all the cases with emphasis on cholecystitis with marked lymphoid infiltration.
Results: Out of 51 cholecystectomy specimens, some rare entities were observed such as 4 cases (8%) of xanthomatous change, 2 cases (4%) of cholecystitis with follicular lymphoid hyperplasia and a case of hyalinizing cholecystitis.
Conclusions: The literature on cholecystitis with marked lymphoid infiltrate (with or without follicle formation) was overlapping and thus confusing. The same has been simplified with review of literature.

Keywords: Cholecystitis, Gall bladder, Follicular hyperplasia, Lymphoid hyperplasia, Lymphoplasmacytic cholecystitis

INTRODUCTION

Gall bladder diseases are common in India causing significant cases of morbidity and mortality. Diseases affecting the gall bladder include nonspecific inflammatory diseases, acute and chronic cholecystitis, granulomatous cholecystitis, follicular cholecystitis, gall bladder polyp, carcinoma/sarcomas along with some rare entities like isolated non-necrotizing granulomatous vasculitis.[1] Because of these diseases there is marked increase in the cases of cholecystectomies which are being performed to cure the symptoms as well as the complications.[2] The present study deals with the nomenclature, prevalence, pathogenesis and diagnostic dilemmas author faced while reporting the cholecystectomy cases with marked lymphoid infiltration (with or without follicle formation) in the wall of the gall bladder. It was also important to rule out lymphoproliferative diseases of gall bladder which can change the face of treatment as well as prognosis of the patient.[3]

A total of 51 cholecystectomy specimens were reported out of which two cases were diagnosed as chronic cholecystitis with follicular lymphoid hyperplasia which is a rare entity with sparse and confusing literature.

METHODS

A total of 51 cases of laparoscopic cholecystectomy were reported in the ITS Histopathology Lab, Greater Noida in a year (2017-2018) duration. These cases were further

evaluated histopathologically to find out various inflammatory patterns giving special attention to lymphocytic infiltration.

Inclusion criteria

Patients of both genders in the age group of 18-65 years showing clinical features of gall bladder disease were included.

Exclusion criteria

Patients not falling in this age group were excluded. In addition, several histologic parameters were assessed in each case, including the type of inflammatory cell infiltrates within the epithelium and lamina propria, cholesterolosis, Rokitansky-Aschoff sinuses, thickening of the muscularis, fibrosis, epithelial hyperplasia, metaplasia and dysplasia. As no granulomatous lesions were encountered during microscopic examinations, so further study by histochemical stains using Ziehl-Neelsen stain for tuberculosis and Periodic Acid Schiff stain for fungal etiology were excluded.[1] The two cases with follicular lymphoid hyperplasia were also sent to outside lab for CD3, CD4, CD8, and CD20 immunohistochemistry in order to rule out the probability of monoclonal proliferation of lymphoid cells. Microbiological analysis for Gram negative bacilli was done to rule out associated infectious etiology. Blood samples were inoculated in blood culture bottles containing trypticase soya broth (HiMedia; 50ml). Incubation, processing and identification of organisms was done as per conventional methods.[4,5] The clinical information and the gross description of the cholecystectomy specimens, were taken from the patient's records.

RESULTS

In the total of 51 cholecystitis specimen, both macroscopic and microscopic patterns with secondary changes were keenly observed (Table 1).

Table 1: Secondary changes in cholecystectomy specimens reported in the study (no case of necrotizing and eosinophilic cholecystitis were observed).

Secondary changes	No. of cases	Prevalence rate
Xanthogranulomatous changes (XGC)	4	8%
Follicular lymphoid hyperplasia	2	4%
Hyalinization	1	2%

Out of these, two cases showed features of chronic cholecystitis with follicular lymphoid hyperplasia. This accounts to a prevalence rate of 4%. Brief information regarding these two cases is given in the Table 2.

Table 2: Information about two cases of chronic cholecystitis with lymphoid hyperplasia.

	Case 1	Case 2
Age	55 years	66 years
Sex	Female	Female
Clinical features	Epigastric pain, nausea vomiting	Epigastric pain, nausea, vomiting, fever
Radiologic findings	Biliary sludge	Small stone
Laboratory findings	CBC and transaminases were within normal range	Leukocytosis with elevated transaminases
Pathologic findings Gross findings	Specimen of gall bladder measured 9.0x2.5cms. Outer surface was unremarkable. Cut section showed the presence of biliary sludge in the lumen. Mucosa was bile stained and exhibited loss of mucosal rugosities at places. Wall of the gall bladder appeared to be slightly thickened.	Cholecystectomy specimen measured 7.5x2.0cms. Cut section showed solitary stone isolated from the fundus measuring 1.0 cm in diameter. Wall of the gall bladder was bile stained and thickened at places. Mucosal rugosities were lost.
Microscopic findings	H and E stained tissue sections revealed normal looking epithelial lining infiltrated by chronic inflammatory cells. At places wall of the gall bladder showed infiltration by monomorphic appearing lymphoid cells in sheets along with few lymphoid follicles with germinal centers. Few large cells with irregular nuclei and minimal cytoplasm were also seen.	H and E stained tissue sections reveal mucosa lined by benign looking epithelial lining showed epithelial hyperplasia and infiltrated by chronic inflammatory cells. At places wall of the gall bladder showed infiltration by lymphoid cells in sheets along with few lymphoid follicles with germinal centers.
Treatment done	Laparoscopic cholecystectomy	Laparoscopic cholecystectomy

Figure 1: Cholecystectomy specimens showing thickened wall and loss of mucosal rugosities in case 1.

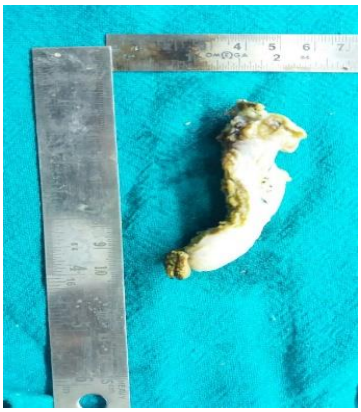

Figure 2: Cholecystectomy specimens showing thickened wall and loss of mucosal rugosities in case 1.

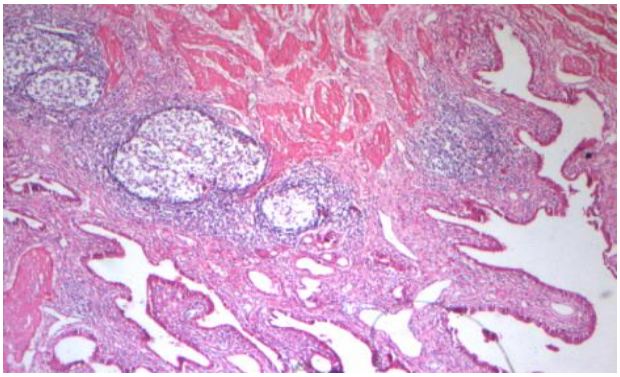

Figure 3: Lymphoid sheets and follicles with germinal center in the mucosa and lamina propria (H&E; 4X).

In the present study, both the patients of chronic cholecystitis with marked lymphoid infiltration were elderly females with a median age of 60.5 years and presented with complaints of epigastric pain, nausea and vomiting. Imaging studies in the first case revealed biliary sludge in the gall bladder while in the second case on ultrasound examination a diagnosis of cholelithiasis was made. Microbiological assay did not show presence of any significant gram-negative bacteria. CD3, CD4, CD8 and CD20 IHC markers were found negative.

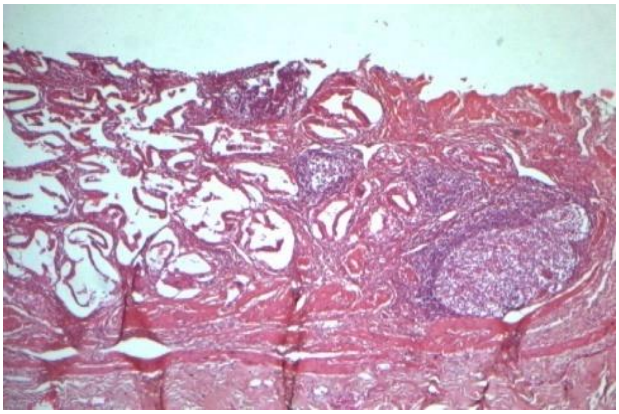

Figure 4: Lymphoid sheets and follicles with germinal center in the mucosa and lamina propria (H&E; 4X).

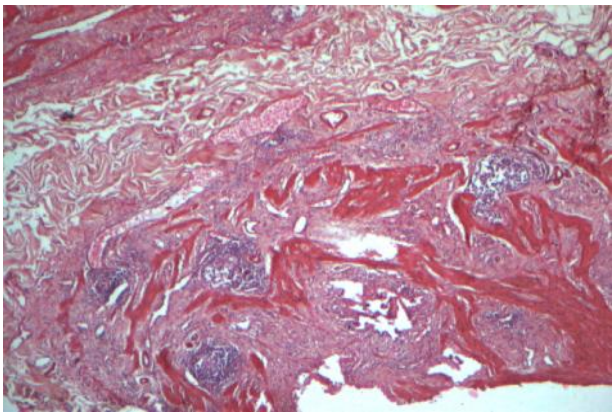

Figure 5: Lymphoid sheets and follicles with germinal center in muscularis propria. (H&E; 4X).

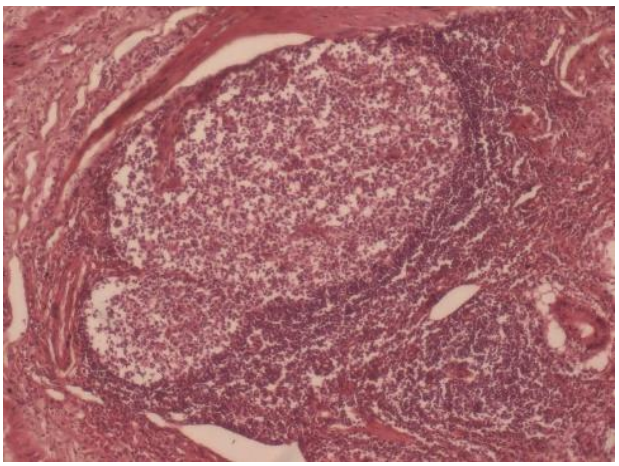

Figure 6: Well-formed lymphoid follicles with germinal center in lamina propria (H&E; 10).

Thus, the results were consistent with reactive/inflammatory change and ruled out lymphoproliferative lesion. Keeping all these findings in mind and after extensive literature review whose elaborative discussion is given below, we made a diagnosis of 'Chronic cholecystitis with follicular lymphoid hyperplasia'.

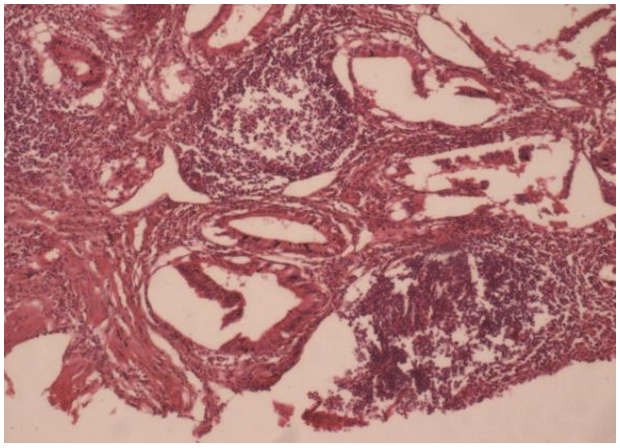

Figure 7: Well-formed lymphoid follicles with germinal center in lamina propria (H&E; 10).

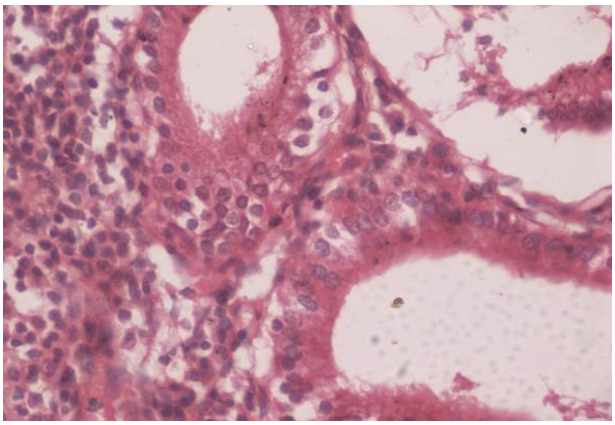

Figure 8: Intraepithelial lymphocytes in mucosa. (H&E; 40X).

DISCUSSION

Chronic cholecystitis is a common condition which is most often accompanied with gallstones. However, about 13% of patients with symptoms of chronic cholecystitis do not have gallstones.[6] In our study, 3 cases (6%) of acalculous cholecystitis were seen which is quite low in comparison to the study by Compton et al.[6]

Recognition of certain inflammatory patterns may require in the identification of the type of inflammatory biliary disease since some types may differ in their pathogenesis and response to treatment. In the present study, 4 cases (8%) exhibited xanthomatous granulomatous change (XGC). The overall global incidence of XGC has been reported to be 1.3-1.9%, with the exception of India where it was 8.8% as per Hale et al which is in accordance to our study.[7]

Only one case of hyalinizing cholecystitis (2%) was seen in our study while a study by Hasan et al revealed about 1.6% cases of hyalinizing cholecystitis amongst the cholecystectomy specimens which is similar to our findings.[8] Hyalinizing cholecystitis is also a rare form of chronic cholecystitis and is said to be associated with risk of gallbladder cancer. No case of necrotizing and eosinophilic cholecystitis was reported in this study.

Amongst the various inflammatory patterns seen in the gall bladder, the concern of the present study is to systematically shed light on the cholecystitis with marked lymphocytic infiltration. Author encountered only two cases (4%) out of the 51 cases examined with this rare form of lymphoid infiltration.

Being a rare entity, literature shows various opinions on this lesion. This study describes the dilemma we faced in the nomenclature, prevalence and diagnosis of cholecystitis with abundant lymphoid tissue in mucosa and lamina propria.

The nomenclature appeared varied, exhaustive and confusing. Lymphocytic cholecystitis/cholangitis, lymphoplasmacytic cholecystitis, follicular cholecystitis, lymph follicular cholecystitis and cholecystitis with lymphoid hyperplasia are few such terms used in the literature. The lymphocytic cholecystitis/cholangitis is the term used for increased number of intraepithelial lymphocytes with >30 lymphocytes per 100 biliary cells instead of normal 3-4 lymphocytes seen in normal gall bladder.

The term lymphoplasmacytic cholecystitis, appears to be associated often with acalculous cholecystitis and histologically presented with diffuse chronic inflammatory infiltrate, with a predominance of plasma cells in the lamina propria accompanied by nodules of mucosal lymphocytes, some of which might have germinal centers.[9] However, the intra-epithelial lymphocytes don't increase.[15]

Follicular cholecystitis characterized by the presence of lymphoid follicles with germinal center.[10] Lymph Follicular cholecystitis is the other term used, which is associated with severe lymphocytic reaction. Cholecystitis with lymphoid hyperplasia is also being used in few cases. However, it has also been mentioned in literature that lymphoid hyperplasia, pseudolymphoma and follicular cholecystitis are some of the synonyms for the same lesion of the gall bladder.[11]

Literature has mentioned that this is an extremely rare disorder. However, in our study of 51 cases of cholecystectomy specimen in one-year period we have seen two such cases, which shows a prevalence rate of 4% in our study. In one study by Gulwani H, M.D.[12] the prevalence rate was 5% which is similar to present study. However, a study by Hatae Y et al mentioned 10 cases among 131 cases of cholecystectomy specimens, which is 7.63% and quite higher than the prevalence rate.[13] Similarly, the sporadic cases of Lymphoplasmacytic cholecystitis shows a prevalence rate of 7% in cholecystectomy specimens.[9] More data on prevalence rate is not available due to rarity of the lesion.

Like nomenclature and prevalence rate, literature shows different diagnostic criteria to diagnose such cases. Few (three to four per 100 biliary cells) intraepithelial lymphocytes are commonly seen in normal gallbladder specimens excised from the donor's liver and used for hepatic transplants.[14] A focal increase in lymphoid cells may be present within the gallbladder epithelium of chronic cholecystitis. However, it is never the predominant inflammatory pattern. A diagnostic criteria of an increased number of intraepithelial lymphocytes, which was taken as >30 lymphocytes/100 biliary cells in one study.[15] When such inflammatory pattern encountered in the stomach, colon, esophagus, and duodenum, it has been called lymphocytic gastritis, colitis, esophagitis, and duodenal lymphocytosis, respectively.[16] By analogy, the term lymphocytic cholecystitis was chosen for this condition. The lamina propria may show lymphocytes to the extent to cause formation of papillae or infoldings which grossly could appear as polyp and thus the term lymphoid Polyp arose.[13,15] Lymphoid tissue in normal mucosa of the gall bladder is very sparse and lymphoid follicles are not seen.[10] In other study by Safia et al, the diagnosis of follicular cholecystitis was based upon the presence of >3 lymphoid follicle with germinal center in 1cm^2 area.[11] However, lymphoid follicles with/without reactive germinal centers should not be observed in the cases of lymphocytic cholecystitis. In this study, author had combined picture showing both these criteria and it was not fitting in any one lesion particularly. Author observed prominent lymphoid follicles with reactive germinal centers, along with scattered intraepithelial lymphocytes (>3-4 lymphocytes which are normally present in cholecystitis), epithelial and muscularis hyperplasia, Rokitansky Aschoff sinuses as well as fibrosis. Keeping all these features in mind we diagnosed both the cases as 'Chronic Cholecystitis with Follicular lymphoid Hyperplasia'. IHC for CD3, CD4, CD8 and CD20 were consistent with reactive change and ruled out lymphoproliferative lesion, which further supports our diagnosis.

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.[17] Another trigger for lymphocytic infiltration may be an autoimmune mediated disorder in other areas of gastrointestinal tract.[18-21] Gram-negative bacterial infection, especially *E. coli* and *K. pneumonia* seemed to be related to severe lymphocytic reactions. None of our cases was associated with a demonstrable infectious etiology.

CONCLUSION

After reviewing the literature, author chose the term 'Chronic Cholecystitis with Follicular lymphoid Hyperplasia'. Diagnostic criteria are given in only two reported cases, which further increased our dilemma to consider all these entity as similar cases or different cases. The prevalence rate in this study seems to be at par with one study while lower than the other study. However, dilemma in prevalence continued as only few cases are reported till date which seconds the rarity of this disease. Due to paucity of data more such studies should be conducted to get a clear picture of this rare disease.

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Ethical approval: Not required

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