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Histologic analysis of chronic inflammatory patterns in the gallbladder

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Abstract
Introduction: *Cholecystectomy is a common surgical procedure. Inflammatory disease is the most common pathology of the gallbladder.*
Objective: *To assess the different morphological changes of chronic cholecystitis in cholecystectomy specimens*
Methods: *Thirty histological specimens from cholecystectomies from patients clear clinical history of biliary lithiasis were histologically evaluated with Haematoxylin-Eosinstaining. Three samples were obtained from fundus, middle third and the neck respectively from each gallbladder.*
Results: *76% of the specimens had metaplastic epithelial changes. Hyperplasia showed a positive correlation (1.0000) with chronic inflammation. Regenerative morphology of epithelial cells was found in 73% of the cases. Regenerative epithelium showed a positive correlation (1.0000) with presence of neutrophils and was significantly associated with mucosal erosions (P=0.005). Fibrosis was observed in all cases (26% mild, 62% moderate, 12% severe). Moderate degree showed a positive correlation (0.999) with severe chronic inflammation. Activity was present in 29% of the cases. Muscular thickness was considered mild in 55% of cases, moderate in 37%, and severe in 8%. Adipose tissue deposits were mild in 47% of cases, moderate in 38%, and severe in 15%. Evolution of the chronic inflammatory cholecystitis was observed in four stages. Initial stage is characterized by mild fibrosis, often with cellular foci, admixed with granulation type tissue in superficial portions of the wall, mild to moderate mononuclear infiltrate and absence of Rockitansky Aschoff sinus(RAS). The second stage consisted of moderate fibrosis and inflammatory infiltrate, often with mild amounts of adipose tissue with RAS extending in to one-third of the length of the specimen. The third stage showed severe fibrosis and chronic inflammation, with moderate to severe adipose tissue deposits with RAS extending in to two-third of the length. The final stage was that of severe fibrosis, often laminated, with reduction ofadipose tissue, a moderate to severe inflammatory infiltrate with RAS extending almost entire length of the specimen.*
Conclusion: *Staging of chronic inflammatory changes in the gallbladder might help in evaluation of the cholecystectomy specimen, to give a rational, systematic, and reproducible diagnosis of different patterns of the inflammatory process.*

I. Introduction

Gallbladder is a frequent surgical specimen[1,2]. Inflammatory disease is the most common pathology of the gallbladder[1].Resection of the gallbladder is performed in two different clinical settings: acute episode of inflammation primarily caused by gallstone obstruction or chronic inflammatory symptomatic disease[1]. A clinical preoperative diagnosis of chronic cholecystitis is commonly made on the basis of suggestive symptoms and confirmed with ultra-sonographic studies that show lithiasis, if present [1,2,3] The role of the pathologist is to determine and name the stage of the inflammatory process (i.e. acute cholecystitis or chronic cholecystitis), establish the presence of gallstones and its nature, describe the presence of associated changes, and search for the presence of incidental carcinoma [3,4]. This study assessed the cholecystectomy specimens which had chronic inflammatory pathology, displaying different morphologic aspects in microscopic observation.

II. Methodology

Retrospective and prospective descriptive study was carried outfollowing histologic analysisof cholecystectomy specimens from thirty patients with clinical history / diagnosis of biliary lithiasis. Specimens were obtained from laparoscopic cholecystectomies done in Colombo North Teaching Hospital and processed in collaboration with the Department of Pathology, Faculty of medicine, Ragama.Data were expressed as frequencies and analyzed using a Statistical Package for Social Sciences 11(SPSS), (SPSS 11.0, Chicago, Illinois, USA). The Specimens were open lengthwise through the serosal lined portion. Longitudinal size, perimeter, and wall thickness were recorded. Three samplesi.e.; one section from the fundus, one of the middle

third, and one of the neck were taken from each gallbladder. The specimens were then routinely embedded and stained. Haematoxylin-eosin-stained slides were reviewed and inflammatory disease was histologically identified in all cases.

Chronic inflammation was diagnosed in the presence of a predominantly mononuclear inflammatory infiltrate, fibrosis, or metaplastic changes[1]. Percentage of metaplastic epithelium in the whole material, less than 70% in a discontinuous fashion was considered focal. Degree of inflammatory mononuclear infiltrate was categorized as mild (diffuse, not more than 10 inflammatory cells per high power field (HPF) in any layer), moderate (diffuse, between 11 to 30 cells per HPF), and severe (diffuse, more than 31 cells per HPF or follicular) [1,2,4]

Ongoing degree of inflammatory activity in chronic inflammation was considered when one or more of these changes were present: erosion (loss of epithelial lining), neutrophilic infiltrate, vascular congestion with foci of neutrophilic margination, epithelial permeation by neutrophils, prominent eosinophilic infiltrate. Three grades of activity were assessed depending on the presence of these histological features: mild activity when only vascular congestion and/or prominent neutrophilswere observed (less than 10 neutrophils/HPF), moderate activity when neutrophilsinfiltrate with permeation (10 to 30 neutrophils/HPF) seen and severe activity when erosion seen with more than 30 neutrophils/HPF [1,2,3,4]

Rockitansky Aschoff sinus formation was observedin four stages in the evolution of chronic inflammatory cholecystitis. An initial stage is of Rockitansky Aschoff sinus(RAS). The second stage consists of RAS extending in to one-third of the length of the specimen. The third stage showed RAS extending in to two-third of the length. The final stage was RAS extending almost entire length of the specimen.

Degree of fibrosis: mild (uneven collagen deposition in ≤ 20% of the material), moderate (uneven collagen deposition in 21% to 70% of the material), and severe (uneven collagen or lamellar fibroplasia in ≥ 71% of the material)[5,6,7]. Thickness of the muscular layer: mildly thickened (less than one third of the whole thickness), moderately thickened (one third to two thirds of the wall), severely thickened (more than two thirds of the wall thickness).

Adipose tissue deposition: mild (up to 10% of the material), moderate (11% to 60% of the material), severe (more than 60% of the material) [8,9]

The quality of changes was also analyzed: Metaplastic changes: pyloric, gastric surface, intestinal. Fibrosis: cellular or fibrous. Additional features were analyzed including intimal thickening of the arteries and neural hyperplasia [5,6,7,10]

III. Results

Degree of inflammatory mononuclear infiltrate was mild in 28%, moderate in 57%, and severe in 15% of cases. A granulomatous reaction was associated in 6.6% cases, those were not florid type with extensive aggregates of histiocytes and multinucleated giant cells in the whole thickness of the wall of the gallbladder. No cases of porcelain gallbladder (diffuse calcification of the wall) were encountered. Moderate degree showed a positive correlation (0.999) with severe chronic inflammation.

Activity was present in 29% of the cases (24.1% with severe activity, 41.4% moderate activity, 34.5% with mild activity). Regenerative morphology of epithelial cells was found in 73% of the cases, 81% of them with confirmed lithiasis, and in all cases with activity. The cells showed reduced height, nuclear hyperchromasia, small nucleoli, and slight to moderate basophilic cytoplasm. Regenerative epithelium showed a positive correlation (1.0000) with presence of neutrophils. The latter were significantly associated with erosion (P=0.005) but not with the presence of lithiasis. Presence of Rokitansky-Aschoff sinuses was observed in 91% of the cases. Rockitansky Aschoff sinus formation was categorized in toin four stages. An initial stage is absences of Rockitansky Aschoff sinus(RAS) (9.9%). The second stage consists of RAS extending in to one-third of the length of the specimen (35%). The third stage showed RAS extending in to two-third of the length (48%). The final stage was RAS extending almost entire length of the specimen (6.6%).

Histologic findings showed that 75% of the specimens had metaplastic epithelial change: 96.7% of pyloric type, 3.3% of intestinal type, and 0% of gastric surface type. Epithelial hyperplasia was observed in 89% of the cases (69.6% of focal type, 30.3% of diffuse type). Hyperplasia showed a positive correlation (1.0000) with chronic inflammation. Neural hyperplasia was associated in 37% of cases, and intimal thickening of arteries was frequently present (67%), usually in elderly patients. Muscular thickness was considered mild in 55% of cases, moderate in 37%, and severe in 8%. Adipose tissue deposits were mild in 47% of cases, moderate in 38%, and severe in 15%. Fibrosis was observed in all cases (26% mild, 62% moderate, 12% severe).

IV. Discussion

We studied the spectrum of changes in chronic inflammatory disease of the gallbladder. Epithelial metaplasia was a common finding. Majority of cases showed a pyloric type distributed in discrete foci, although a large percentage showed diffuse metaplastic change. Metaplasia is a strong supportive factor for the diagnosis

of chronic cholecystitis. Although the presence of metaplasia was associated with chronic changes, the extent of metaplasia did not correlate with fibrosis or amount of inflammatory change, so its production seems to be pathogenically independent and related to genetic predisposition or other contributing factors[7,8,9,10]

Regenerative changes in the epithelium were found in two different conditions. One condition was associated with epithelial erosion or mucous ulceration that always showed neutrophils. The other condition was associated with gallstones, whose presence is not associated with the presence of neutrophils. It has been reported that lithiasis *per se*, or the biochemical imbalances that contribute to its production, are an insult to the epithelium [5,6]. One or both conditions could damage epithelial cells, producing an increase in renovation associated with a regenerative phenotype. But the presence of neutrophils is determinant in the pathways that led to epithelial damage and/or regeneration. The acute inflammation drives the expression of endothelial cell adhesion molecules and integrinsthat recruit neutrophils in inflammed tissues, which also close the circle adding more damage to epithelial cells [11]The presence of neutrophils correlated with epithelial erosion but not with the presence of lithiasis, although the latter was commonly associated with epithelial damage. Mucosal neutrophils within the lamina prophria are strong predictors of simultaneous erosion, which could be observed in representative sections.

Lymphocytes are an intrinsic part of the chronic cholecystitis, as they are included in the definition [1]. Long-standing forms of cholecystitis are prone to exhibit a B-lymphoid infiltrate, and, when activity is present, T lymphocytes are restricted to damaged areas [5,6,7]

Fibrosis could be observed in different evolutionary states, sometimes coexisting. As in other tissues, granulation-type reaction follows or is simultaneous with acute episodes of inflammation. Collagenous deposition begins early. At first, collagen fibers are unevenly distributed, a feature of the disordered fibrosis, which also shows a large number of fibroblasts. Second, an ordered deposition of collagen fibers takes place, which constitutes the lamellated fibrosis seen at more advanced stages of the chronic cholecystitis. The same is true for calcification (porcelain gallbladder), which was not observed in our series but was a frequent finding in older reviews when the surgical treatment was performed in long-standing disease [7,8,9,10,11]

The signs of lithiasis are the presence of yellowish pigment adhered to the surface epithelium or inside the lumen of Rokitansky-Aschoff sinuses, or even included within the wall. When pigment or cholesterol chrystals are surrounded by giant cell-histiocytic reaction the appropriate term to design the condition is *xantogranulomatous cholecystitis*,and thus is diagnosed referring to a special kind of inflamatory process with prominent intake of biliary substances by the wall or mechanical penetration of them. In some cases, (one in our series), the reaction is so florid that the wall of the gallbladder is thickened, its consistency increased, and a wrong diagnosis of carcinoma is frequently made by the surgeon [12].

In our study, we observed four stages in the evolution of chronic inflammatory cholecystitis. An initial stage is characterized by mild fibrosis, often with cellular foci, admixed with granulation type tissue in superficial portions of the wall, mild to moderate mononuclear infiltrate with absence of RAS. The second stage consists of moderate fibrosis and inflammatory infiltrate, often with mild amounts of adipose tissue with RAS extending in to one-third of the length of the specimen .The third stage shows severe fibrosis and chronic inflammation, with moderate to severe adipose tissue deposits with RAS extending in to two-third of the length .The final stage is that of severe fibrosis, often laminated, with reduction of adipose tissue except in peripheral localizations, a moderate to severe inflammatory infiltrate that is mild in few cases with RAS extending almost entire length of the specimen and in some cases with dystrophic calcification which was not found in our study leads to the so-called porcelain gallbladder. The latter condition is unusual in current practice because of the increase in prompt resections /early surgical intervention [13,14]

Therefore, chronic inflammatory cholecystopathy shows a morphologic spectrum that exhibits signs of an inflammatory process at every stage in its evolution. In keeping with literature we also found that whatever the injury (chemical, physical, or biochemical), the process seems to be stereortipical[14].

V. Conclusion

We consider that the staging of chronic inflammatory changes in the gallbladder might help in evaluation of the cholecystectomy specimen, to give a rational, systematic, and reproducible diagnosis of different pictures of the inflammatory disease.

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