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メタデータ	言語: 出版者: 琉球医学会 公開日: 2010-07-02 キーワード (Ja): キーワード (En): adenomyomatosis, histological typing, associated gallstone, gallbladder 作成者: Tokumine, Fumio, Muto, Yoshihiro, Kusano, Toshiomi, Tomita, Shuji, Isa, Tsutomu, Toda, Takayoshi メールアドレス: 所属:
URL	http://hdl.handle.net/20.500.12000/0002015894

Adenomyomatosis (Intramural Diverticulosis) of the Gallbladder : A Clinicopathological Study of 197 Cases

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(Received on April 14, 1993, accepted on November 30, 1993)

ABSTRACT

One hundred and ninety-seven cases of adenomyomatosis of the gallbladder were clinicopathologically studied. Our histologic criterion for adenomyomatosis was based on a "gallbladder wall thickness of greater than 3mm secondary to proliferation of 5 or more Rokitansky-Aschoff sinuses (RAS) per 1cm-length of the wall". Depending on the location of the lesion, adenomyomatosis was divided into four types : fundal, segmental, combined (fundal and segmental) and generalized. The incidence of this disease was 10.7% in a series of consecutive cholecystectomies. The average age at cholecystectomy was 52.1 years. There was preponderance of male in a ratio of 1 to 0.88. The two commonest types were segmental and fundal, accounting for more than 80% of the disease. The average age in each type was similar. The overall incidence of associated gallstones and intramural calculi was 85.8% and 46.7%, respectively. Grossly, all types showed essentially a thickening of the involved wall with their own pathologic features. Histologically, they represented an identical proliferation of the RAS, a thickness of the muscularis and a frequent clustering of the epithelium. The two latter components, however, were not invariable. *Ryukyu Med. J., 14 (1) 17 ~ 23, 1994*

Key words : adenomyomatosis, histological typing, associated gallstone, gallbladder

INTRODUCTION

Epithelial lined sinuses (hernia-like outpouchings of the mucosa) are usually found in the gallbladder wall. These sinuses are generally known as Rokitansky-Aschoff sinuses (RASs)¹⁾. The RASs that do not penetrate as far as the muscularis are accepted as being normal structures. The RASs show also their penetration into the muscularis and expansion outside the muscularis^{2,3)}. These deep RASs are believed to be pathologic. They never project beyond the serosal surface⁴⁾. Thus, the RASs have been termed "intramural diverticula" as an alternative nomenclature. The RASs constitute the basic and essential feature of adenomyomatosis. In a typical form, this disease is histologically characterized by excessive proliferation of the RASs in association with so-called hyperplasia of the surface epithelium and thickening of the muscularis. Adenomyomatosis of the gallbladder has been accepted as a clinical entity, preferably by radiologists⁵⁻¹⁰⁾. Nevertheless, any pathologic criterion for this disease has not been clearly established.

The purpose of this study was three-fold: (1) to propose a histopathologic criterion for adenomyomatosis, (2)

to present a clinicopathologic study of 197 cases, and (3) to discuss developmental process of the disease.

MATERIALS AND METHODS

The surgically removed gallbladders were sliced serially after fixation. All of the specimens were processed in the routine manner for histologic examination. Of 1,841 cases at the Hamamatsu Medical Center (1980-90) and the Ryukyu University Hospital (1985-92) reviewed histological data, 197 cases have fulfilled our histologic criterion as described later. In this report clinical manifestations and follow-up studies are not presented.

Histopathologic Criterion

Thirty segmental types of macroscopic adenomyomatosis that fit our histologic criterion of annular, diffuse thickening of the wall of the involved segment were randomly selected. Grossly, the gallbladder revealed identical stenosis of the lumen and thickening of the wall of the involved segment without any evidence of inflammation. Two or three tissue sections were taken from the involved segment, the RASs were counted and wall thick-

ness was measured on histologic slides. The average number of the RASs in 1 cm-length of the involved wall per case was 5.9 ± 0.8 and wall thickness averaged 3.2 ± 0.3 mm. Based upon this data, we have defined adenomyomatosis as "gallbladder wall thickness of greater than 3mm exclusively due to proliferation of 5 or more RASs per 1 cm-length of the wall".

Typing of Adenomyomatosis

Typing of this disease according to its location is very important because each variety has its own pathologic pattern which may help in diagnosis. From a clinical and pathological perspective, we classified the disease into four types as follows:

- (1) Fundal or localized type (F-type), which involves locally the distal tip of fundus. In invagination, this type gives rise to a characteristic doughnut-like nodule.
- (2) Segmental or annular type (S-type), which occupies one or more fairly discrete segments (commonly in the neck or body).
- (3) Combined type (C-type), consisting of two types of lesion. In this type, a rather abrupt demarcation between S-type and F-type is commonly evident.
- (4) Generalized or diffuse type (G-type), which involves nearly or the entire gallbladder.

RESULTS

Incidence

This study was based on 197 cases which were diagnosed by our histologic criterion for adenomyomatosis in a series of 1,841 consecutive cholecystectomies, representing an incidence of 10.7%.

There is a wide incidence variation reported in the literature, accounting for 0.5% to 33.3%^{6,7}, mostly 2% to 5%. This variability may depend upon whether the search for the disease was prospective or not, and difference of histologic criterion. The latter may be more significant in establishing the diagnosis of a morphological alteration of the disease.

Age and Sex

The age at the time of cholecystectomy ranged from 26 to 83 years with an average age of 52.1 years. Six patients were in the second decade, 32 in the third, 50 in the fourth, 60 in the fifth, 36 in the sixth, 10 in the seventh and 3 in the eighth (Fig.1).

When stratified by age, the incidence of adenomyomatosis in general cholecystectomies was 3.6% in the second decade, 15.0% in the third, 12.7% in the fourth, 12.8% in the fifth, 9.8% in the sixth, 3.1% in the seventh and 5.0% in the eighth. The incidence has been documented to increase with age in the literatures^{6,8-10}. However, this correlation was not observed in our series.

There were 105 males and 92 females; a male to female ratio of 1 to 0.88. On the contrary, the sex ratio of male to female in our general cholecystectomies was 1

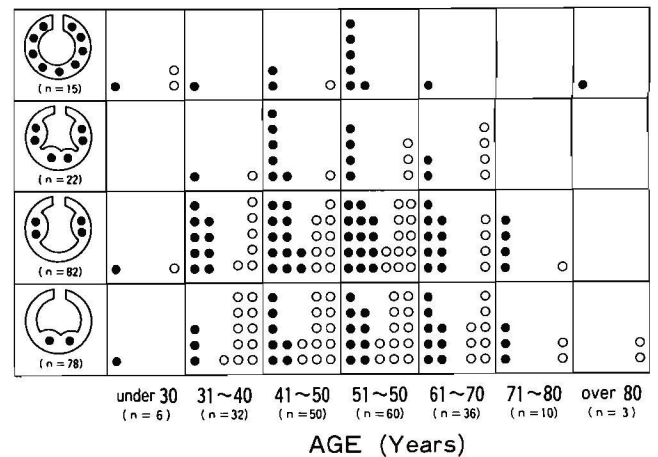


Fig. 1. Age and sex distribution in each type (closed circle; male, open; female).

to 1.8. Therefore, the males were two times more than the females. It is generally accepted that adenomyomatosis is more common in females than in males. The sex ratio in this series is quite different from those reported in the literatures⁸⁻¹⁰. Such difference in sex ratio is currently difficult to explain even allowing for surgical selection or a difference of histologic criterion.

Correlation of Type to Age and Sex

Of 197 cases, seventy-eight (39.5%) were fundal, 82 (41.6%) segmental, 22 (11.2%) combined and 15 (7.6%) generalized.

The average age in each type was 51.1 years in the F-type, 52.2 years in the S-type, 55.3 years in the C-type and 50.6 years in the G-type (Fig. 2). There was no significant age difference among the four types. Generally, adenomyomatosis has been considered as a slowly progressive process that produces its own pathologic feature in the advanced stage. This concept may lead us to believe that as the disease progresses, the lesion in a given gallbladder spreads steadily with aging. Nevertheless, any description concerning the evolution of localized lesion to diffuse one has not yet been reported. This consideration may lead to the hypothesis that when some anatomic changes start to take place at a certain location at the initial stage, these alterations confine to the original location, and then gradually develop the lesion into own pathologic lesion of each type in the advanced stage.

The relation of each type to sex ratio of male to female was 1 to 1.52 in F-type, 1 to 0.67 in S-type, 1 to 0.69 in C-type and 1 to 0.25 in G-type. From this result, the S-, C- and G-types occurred more frequently in male than in female.

Associated Gallstones and Intramural Calculi

The incidence of associated gallstones and intramural calculi was 85.8% and 46.7%, respectively. The incidence of associated gallstones, their anatomic locations and in-





					Total
No. of Cases	78	82	22	15	197
Sex Ratio	M31 : F47 1 : 1.52	M49 : F33 1 : 0.67	M13 : F9 1 : 0.69	M12 : F3 1 : 0.25	M105 : F92 1 : 0.88
Age (years)	28-77 51.1	31-76 52.2	38-70 55.3	26-83 50.6	26-83 52.1
Type	Fundal or localized	Segmental or annular	Segmental + fundal	Generalized or diffuse	

Fig. 2. Correlation of type with number of cases, sex ratio and average age.

tramural calculi in each type are shown in Fig. 3. This higher incidence of associated gallstones depended upon surgical selection. The vast majority of our gallbladders were surgically removed because of gallstones.





Pathologic Findings

(1) Fundal (F) type

The lesion presented its typical features in full invagination of the gallbladder, showing a circular, sessile nodule with a central crater-like dimple that simulates the shape of a doughnut (Fig. 4). The nodule was elevated few to several millimeters above the surrounding mucosa depending upon the degree of invagination. The diameter ranged from 7 mm to 20 mm, with an average diameter of about 10 mm. The consistency of the nodule was that of the normal lymph node at the time of cholecystectomy or in the fresh, resected gallbladder.

The cut surface of the nodule throughout the the central umbilication revealed the yellow-white nodule with tiny cavities representing the RASs, resembling a sponge on cut section (Fig. 5). Overgrowth of the surface epithelium restricted to the lesion appeared to increase the number and height of folds, and often gave a velvety appearance to the mucosal surface. We believe that this type is a variety of S-type localized at the fundus with special features derived from its location.

Histologically, the average lesion was composed of proliferation of the RASs, hyperplasia of the surface epithelium and thickening of the muscularis (Fig. 5, Bottom). The RASs were tubular or cystic depending upon the degree of their penetration. The RASs above the muscularis were tubular, while the deeply seated RASs below the muscularis were cystic. These RASs often showed branchings. The channel of communication between the lumen of the gallbladder and that of the cystic RASs was stricured by the muscularis. The lining epithelium of the

	 (n=78)	 (n=82)	 (n=22)	 (n=15)	Total (n=197)
Calculous Cases	62 (79.5)	74 (90.2)	21 (95.4)	12 (80.0)	169 (85.8)
GB	50 (80.6)	60 (81.0)	17 (80.9)	9 (75.0)	136 (80.5)
GB + CD	9 (14.5)	12 (16.2)	4 (19.0)	3 (25.0)	28 (16.7)
CD	2	1	0	0	3
IH	1	1	0	0	2
Acalculous Cases	16 (20.5)	8 (10.8)	1 (0.45)	3 (20.0)	28 (14.2)
Intramural Calculi	23 (29.5)	45 (54.8)	13 (59.0)	11 (73.3)	92 (46.7)

() : %

Fig. 3. Correlation of type with associated gallstones and intramural calculi. (GB; gallbladder, CD; common duct, IH; intrahepatic).

tubular RASs was columnar analogous to the surface epithelium. When the RASs were cystic and frequently filled with bile or genuine calculi, the lining epithelium of the RASs became flattened or eroded. There were more or less inflammatory reaction around the RASs. When the mucosa of the lumen revealed metaplasia, the lining epithelium of the RASs often accompanied metaplasia.

In addition to proliferation of the RASs, the lesion frequently showed hyperplasia of the surface epithelium and thickening of the muscularis. It is important to recognize the fact that the normal gallbladder wall seldom exceeds more than a few mm thick. In our series, G-type reached several times the normal thickness, representing 5 to 10 mm thick on histologic sections. Although all histologic layers were involved in this process, the degree of the thickening of the wall depended mainly on the number of the RASs and the presence or absence of the cystic RASs. The surface epithelium confined to the lesion developed folds. The folds increased in number and height, preserving their own structures with no evidence of atypia. Generally the muscularis was mostly thick just beneath the surface epithelium, and could be traced at a gradually increasing distance from the surface epithelium. There were rarely the muscular fibers evident around the deeply seated RASs.

(2) Segmental (S) type

This type occurred usually in a limited area of the neck or body, showing an annular stricture of the lumen with the thickening of the wall. When the annular section of the wall was involved a few to several mm wide, the lesion gave rise to septum-like bulging into the lumen such as a congenital septum. When it was involved more than 1 cm wide, the lesion showed stenosis of the lumen and thickening of the wall (Fig. 6, Top). The stenosis of

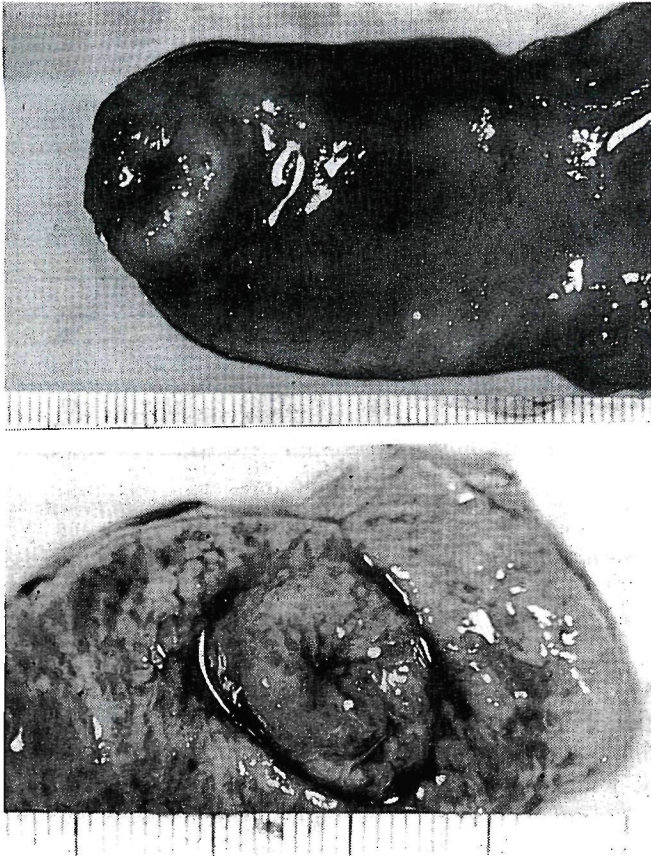


Fig. 4. Macrophotographs of F-type showing a circular, sessile nodule with a central umbilication (Top; in full invagination, Botom; in the opened gallbladder), simulating the shape of a doughnut.

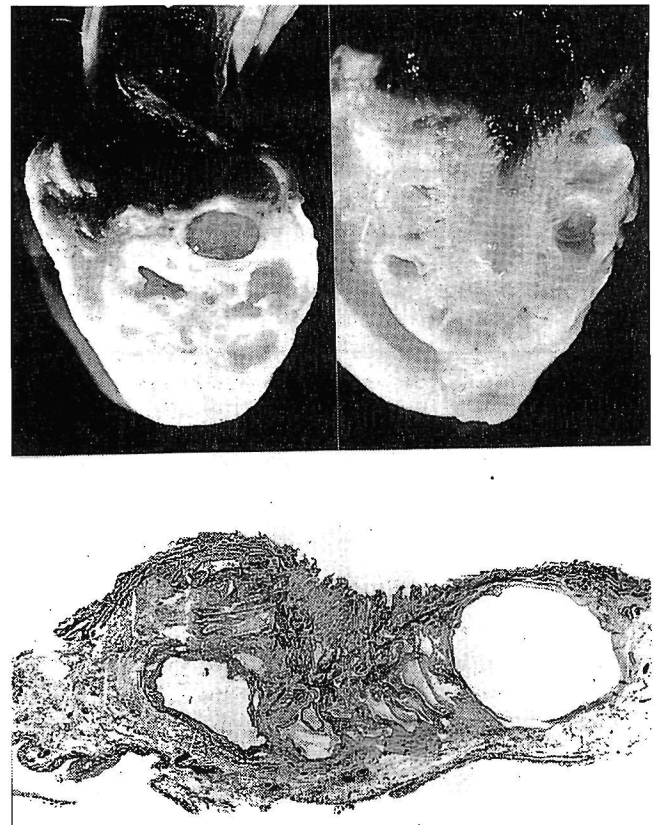


Fig. 5. Macrophotographs of cut surface and microphotographs of F-type showing a nodular thickening of the wall at the tip of the fundus (Top) and revealing a typical histologic feature (Bottom, HE, $\times 2.5$).

the lumen was dependent upon the degree of thickness of the wall.

(3) Combined (C) type

The C-type was composed of the two lesions, S- and F-type in a given gallbladder. Commonly the normal tissue was evident between both (Fig. 6, Bottom).

(4) Generalized (G) type

The lesion of this type spreads the total or nearly total gallbladder. This presented a normal shape of the gallbladder with increased wall thickness and reduced lumen (Fig. 7).

DISCUSSION

Adenomyomatosis of the gallbladder has been widely accepted as a hyperplastic conditions^{5-7,9,10}. Our discussion is concerned principally with developmental process of adenomyomatosis in considering its morphological features and etiologic concepts.

Anatomically the gallbladder is a variety of the bile ducts and composed of four layers^{11,12}, mucosa, muscular-

is, subserosa and serosa. There are no true lamina muscularis mucosae and submucosa, and the wall is very thin. These histological features of the gallbladder are distinguishable as compared with those of the gastrointestinal tract. The muscularis is a network of smooth muscle fibers running in multiple directions, often loosely packed with small gaps through which nerves and blood vessels pass. Based on our study on the RAS¹⁰, the average gallbladder had one RAS in size of 1cm² of the wall. They are not regarded as particularly abnormal structures. Especially when the proliferating RASs are associated with thickening of the muscularis and other wall tissues through which they penetrate, the total lesion takes on the pathologic picture intended by the term "adenomyomatosis".

An increased thickness of the wall is the most characteristic feature in the disease. The involved wall reaches three to several times the normal thickness. Jutras *et al.*^{6,7} have described that in adenomyomatosis the muscularis is three to five times thicker than normal and their description on this entity has described details with the radiographic diagnostic features, but not with the histolo-

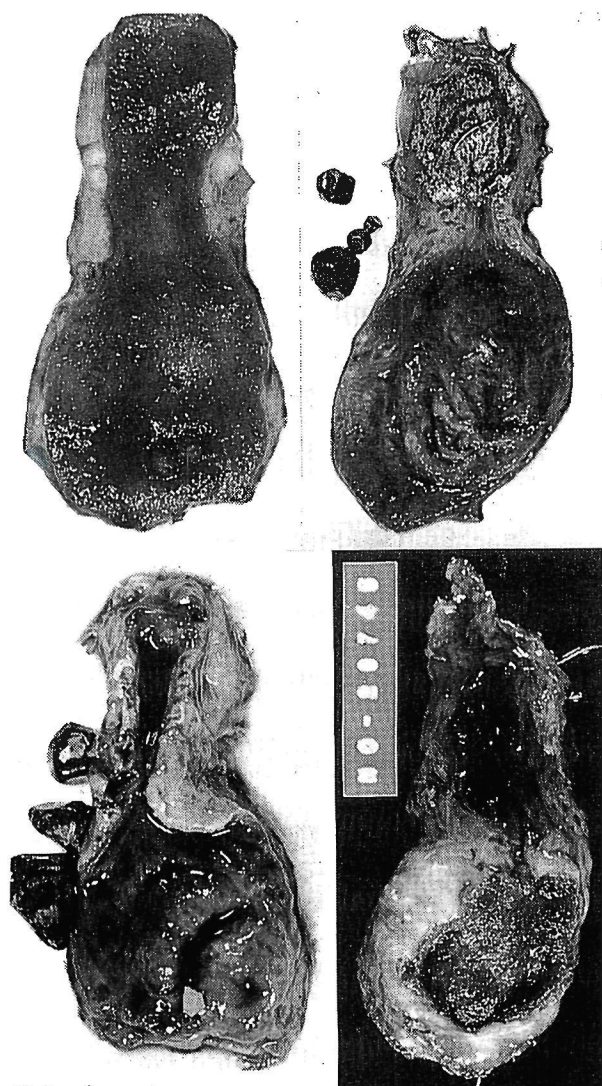


Fig. 6. Macrophotographs of S- and C-types showing an annular stenosis (Top, left) and a septum-like stricture (Top, right) in S-type and similar features in C-type (Bottom).

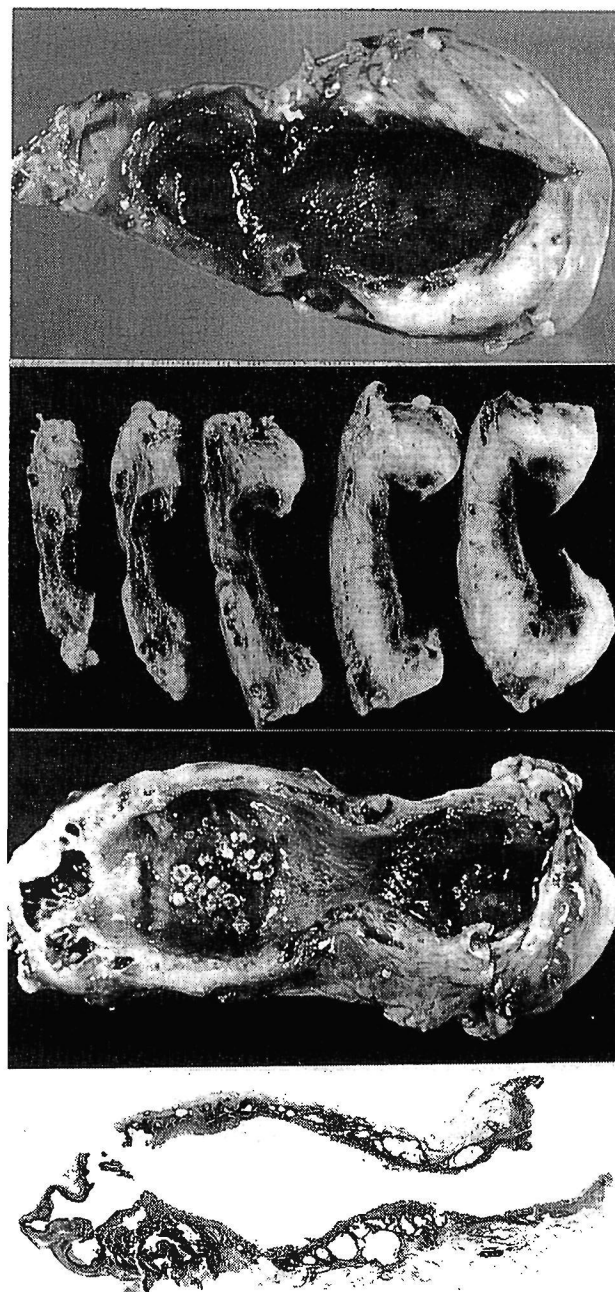


Fig. 7. Macrophotographs of G-type showing markedly thickened wall (Top) and cystically dilated RASs (Bottom).

gical findings.

In all types of adenomyomatosis, the lumen of the gallbladder can be recognized to be comparably reduced in size depending on the degree of thickening of the involved wall. This is best exemplified in the S-type. In general, all layers of the wall may be involved in the wall thickening, but thickening of the muscularis is one of the causes for thickening of the wall. Nevertheless, muscular thickness alone is not sufficient for a given gallbladder to be diagnosed to have adenomyomatosis. Therefore, the RASs are absolutely inevitable components in the definite diagnosis of adenomyomatosis. Thus, it is reasonable to postulate that the RASs may play a primary exclusive role in the evolution of the disease.

If the RASs proliferate in the wall, why does the wall become thicker and more contracted? As aforementioned,

the RASs are hernia-like outpouchings of the surface epithelium through the muscularis into the subserosa. To understand precisely the developmental process of adenomyomatosis, it must be appreciated that since the lamina propria mucosae is directly attached to the muscularis, the shape and size of the surface epithelium may directly depend upon the existing phase of contraction of the gallbladder. Accordingly, as the RASs increase in number and depth, the surface epithelium becomes reduced in its size and then the surface epithelium among the RASs may

be tensed. Eventually the wall becomes thicker by means of tensile strength of the surface epithelium resulting in stenosis or size reduction of the lumen. At the same time, the muscularis becomes closely packed together as a result of traction exerted by the RASs. The surface epithelium also become condensed, showing an increased number and height of folds, especially in the F-type, intended by the term "hyperplasia".

The muscularis has been generally regarded as one of the main components of adenomyomatosis, but thickening of the muscularis is not invariable. Even in a typical lesion, with distance from the surface epithelium the muscle fibers become traced or frequently absent in the lesion. If this disease is a hyperplastic complex of the muscularis as one component, the lesion should reveal an even distribution of the muscle fibers. If thickness of the muscularis represents a true hypertrophy, enlargement of muscle cells and nuclei should be demonstrated. Nevertheless, there was no histopathologic evidence favoring true hypertrophy of the muscularis in this study and any description on this subject has not been described in the literatures. Thus, it should be considered that thickening of the muscularis accounts for a close packing of the muscles in a limited length of the gallbladder wall, a condensation rather than a pathologic process of hypertrophy of the individual muscle cells as a result of traction by development of the RASs.

In a same manner, we believe that hyperplasia of the surface epithelium described herein and in the literatures represents a condensation rather than a hyperplasia. These considerations may lead us to accept an increasing belief that proliferation of the RASs is of prime importance in the development of adenomyomatosis of the gallbladder, and so-called hyperplasia of the surface epithelium and muscular thickening are secondary phenomena due to proliferation of the RASs. Therefore, we prefer to accept the term "diverticulosis" rather than "adenomyomatosis" as the most logical inclusive term for the complex process of this disease.

With regard to etiology of adenomyomatosis, several theories^{5-7,13-15)} have been proposed in the literatures. In one case; the diverticula of the intestinal tract and the bladder¹⁶⁾, the cause of the RAS is due to primarily to an increase in pressure of the gallbladder. Physiologically one of the important roles of the gallbladder is to deliver bile into the duodenum, emptying the gallbladder when intraluminal pressure is significant. In studies on the human biliary tract, resistance to flow from the gallbladder to the cystic duct was found to be 11 to 20 cm of water¹¹⁾. It is appreciated that a considerable pressure necessitates emptying of the gallbladder. Anatomically the gallbladder has distinguishable structures; lack of the lamina muscularis mucosae and the thin, loosely packed muscularis. These characteristics favor development of diverticula, the RASs of the gallbladder by its intraluminal pressure. With presently available information on etiology, we have an increasing belief that increased intralu-

minal pressure of the gallbladder is the first step toward RAS formation. From this etiologic stand point, it is of curious as to why the RASs never project beyond the serosal surface. This characteristic feature of the RASs as compared with diverticula of the intestinal tract may derive from the anatomy of the gallbladder. As mentioned above, the surface epithelium is directly and intimately attached to the muscularis. Accordingly, the RASs may never project beyond the serosal surface. Finally, taking our data and discussion on the disease into consideration, we may hold the view that adenomyomatosis of the gallbladder is a diverticular disease caused by intraluminal pressure of the gallbladder. The RASs play a primary exclusive role in the development of the disease, and so-called hyperplasia of the surface epithelium and thickening of the muscularis are a merely secondary alteration.

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