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Adenomyomatosis of the Gallbladder: A Clinical Survey of
30 Surgically Treated Patients

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Abstract

Thirty patients with adenomyomatosis of the gallbladder (AMG) were operated on between January 1983 and June 1990. They were made up 3.3% of patients who underwent cholecystectomy during the same interval. Of the 30 patients, ages ranged from 22 to 77 years (mean 52.3 years) and the male-to-female ratio was 8 : 7. Among the macroscopic types, 10 cases of generalized, 12 of segmental (S) and 8 of fundal (F) were noted, and the size of the affected portion in type S (0.8 ± 0.2 cm, mean \pm SD) was significantly thinner than in other two types ($p < 0.05$). Although the main symptom was abdominal pain, the majority of patients with type F had no complaints. Twenty patients (27%) were accompanied by gallstones including cholesterol stones in 60% of cases, and all six cases showing microbes in the bile had gallstones. Only six patients were diagnosed as AMG by preoperative imaging techniques. Other diagnoses comprised 15 of chronic cholecystitis and 3 of suspected gallbladder carcinoma. To identify the expanded Rokitansky-Aschoff sinuses, endoscopic retrograde cholangiography and/or ultrasonography of the abdomen were most useful. No preponderant coexistent lesion other than gallstones was noted. Levels of carcinoembryonic antigen in gallbladder bile in cases of AMG (2.5 ± 1.5 ng/ml, mean \pm SD) were significantly lower than in gallbladder carcinoma ($p < 0.01$). All the patients were easily treated with cholecystectomy, and 24 patients who have been followed up after surgery are doing well. These 30 patients with AMG accounted for 11.2% of 269 patients who showed thickening of the gallbladder wall of 3 millimeters or more in the present survey. Not only the patients accompanied by gallstones but also acalculus patients with some symptoms or with suspected malignancy should undergo surgery for AMG.

Key words: Gallbladder adenomyomatosis, Rokitansky-Aschoff sinuses, Gallbladder wall thickening, Acalculus adenomyomatosis, Bile carcinoembryonic antigen.

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Introduction

Adenomyomatosis of the gallbladder (AMG) is a condition characterized by partial or total thickening of the gallbladder wall due to hyperplasia of the mucosa, thickening of the muscular layer and overgrowth of ROKITANSKY-ASCHO sinuses (RAS)³⁾. The proliferated RAS that is essentials of AMG²²⁾, show multiple intramural diverticula, cysts or sinus tracts. Distinguishing AMG from malignancy before or during surgery is occasionally difficult.

In 1931, KING and MACCALLUM¹⁶⁾ used the term cholecystitis glandularis proliferans in consideration of the inflammatory nature of AMG. Since then, several hypotheses including benign tumor, dysplasia and myoepithelial anomaly, have been published to account for the pathogenesis of AMG⁷⁾. In 1960, JUSTRAS et al.¹²⁾ introduced hyperplastic cholecystoses, which indicated non-neoplastic proliferation and non-inflammatory change of the usual histology of the gallbladder, and in 1962 *Jutras*¹³⁾ classified cholecystoses into the five conditions; adenomyomatosis, cholesterosis, neuromatosis, elastosis and hyalinocalcinosis. Only the former two are worthy of further discussion at present³⁾.

AMG is divided into three macroscopic types with regard to the site and degree of RAS-proliferation^{3,6,7,12)}; generalized (G) or diffuse type with entire wall thickening and luminal narrowing of the gallbladder (Fig. 1-A), segmental (S) or annular type with focal circumferential narrowing and compartmentalization (Fig. 1-B), and fundal (F) or localized type mainly showing intraluminal elevation at the fundus with occasional central umbilication (Fig. 1-C). Further classifications also have been described^{1,20,22,33)}.

In Japan, according to a collective review by MIYAOKA et al.²¹⁾, a total of 236 cases of AMG have

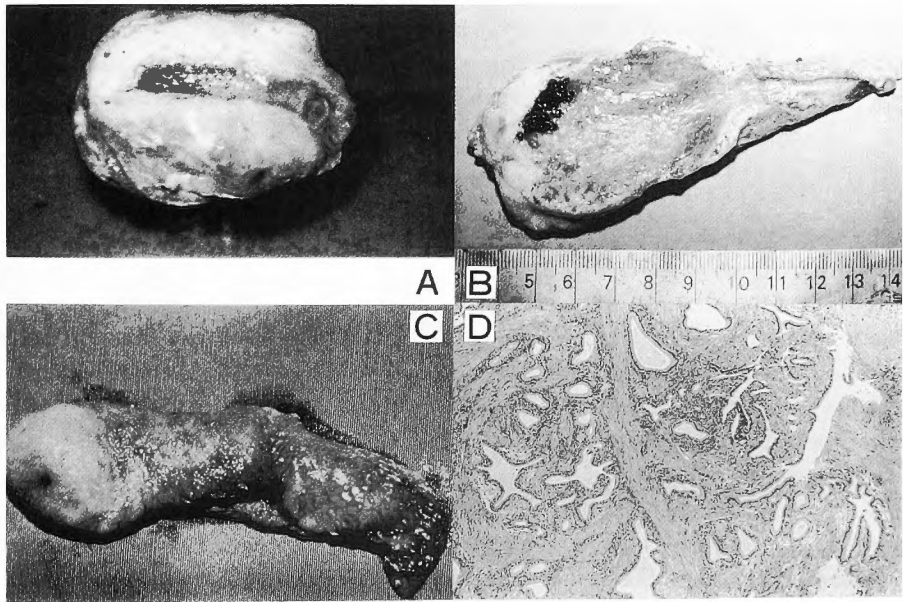


Fig. 1 Adenomyomatosis of the gallbladder; A: marked wall thickening and luminal narrowing in generalized type, B: specimen of segmental type accompanied by gallstones and fundal adenomyomatosis, C: central umbilication in fundal type and D: photomicroscopic findings of overgrown Rokitansky-Aschoff sinuses (H-E, $\times 40$)

been reported between 1970 and 1980. In 1985, MUTO²²⁾ made a clinicopathological survey of 109 patients and in 1988 UCHIMURA et al.³³⁾ studied 131 patients. Although AMG has been recognized to be a definite condition separate from the uncertain category of chronic cholecystitis²²⁾ and reported cases have increased, controversies surrounding the clinical significance and management of this condition still remain. Therefore, we also studied patients with AMG on the basis of our surgical experience.

Patients and Methods

A total of 896 patients who underwent cholecystectomy for benign or malignant lesions in our clinic between January 1983 and June 1990 were included in this study. These patients consisted of 459 men whose ages ranged from 21 to 88 years and 437 women ranging from 16 to 86 years with prevalence of the sixth and seventh decades of life for both sex. There were 654 gallstone patients (296 men and 358 women) and 242 acalculus patients (163 men and 79 women). Clinical charts including reports of diagnostic imaging techniques, surgical records, sketches or Polaroid color prints of the resected gallbladder and results of pathohistology were studied for all patients.

In order to determine the presence of AMG, we adopted MUTO's guideline²²⁾ for five or more proliferated RAS within one centimeter of the gallbladder wall and wall thickening of a size of 3 millimeters or more. Histology of the RAS in a typical case of AMG is shown in Fig. 1-D. Prior to cholecystectomy, gallbladder bile was aspirated for cultures of microbes for the majority of patients. The bile from eight patients affected by acalculus AMG was used for the determination of levels of carcinoembryonic antigen (CEA, ng/ml), CA19-9 (U/ml) and pancreatic secretory trypsin inhibitor (PSTI, ng/ml) by radioimmunoassay. For the control, the bile of six patients having gallbladder carcinoma of an elevated type were also analyzed for levels of these three tumor markers. The composition of gallbladder stones were analyzed by infrared photospectrometry.

Data are expressed as means \pm SD. Statistical analyses were made using *Student's t*-test. A *p* value less than 0.05 was considered significant.

Results

Wall thickening of the gallbladder by 3 millimeters or more was noted in 269 patients, and finally 30 patients were diagnosed as having AMG. Their clinical symptoms, types of AMG, and coexistent diseases are summarized in Table 1. Of 30 patients of AMG (3.3% of all those cholecystectomized), their ages ranged from 22 to 77 years (52.3 ± 11.9 years) and the male-to-female ratio was 8 : 7. With regard to the site affected by AMG, 10 were of G type, 12 were of S type and 8 were of F type. A cross section of the most involved portion in S type (0.8 ± 0.2 cm) was significantly thinner than that of the other two types ($p < 0.05$, in each), (Table 2).

Main preoperative symptoms of the gastrointestinal tract were 18 cases of abdominal pain, 10 of abdominal discomfort and 2 of appetite loss, and six patients (20%) were symptom free. Regardless of the presence or absence of accompanying gallstones, AMG was suspected in 6 patients using ultrasonography (US) of the abdomen and/or endoscopic retrograde cholangiography (ERC) before surgery. Other diagnoses were 15 cases of chronic cholecystitis, 5 of cholesterosis or benign polyp or 3 of gallbladder carcinoma (Table 2). A 54-year-old man was incidentally found to have AMG of F type at surgery for hepatocellular carcinoma.

Twenty-four patients underwent simple cholecystectomy, and six were added further procedures because of coexistent lesions. Rapid intraoperative pathology of the gallbladder was performed in 10 patients to distinguish findings from malignancy. Twenty patients (67%) of AMG had cholelithiasis consisting of 12 cases of cholesterol stones, 5 of bilirubin stones, 2 of black stones and one of calcium phosphate. Five cases of bilirubin stones and one of cholesterol stones showed infected bile. Although various coexistent diseases in the hepato-biliary-pancreatic system were noted, no notable lesion other than gallstones was present. Analyses of bile for three tumor markers revealed that CEA in the gallbladder carcinoma was of a significantly higher level (25.7 ± 7.1 ng/ml) than in AMG (2.5 ± 1.5 ng/ml), ($p < 0.01$), (Table 3).

Table 1 Each type of adenomyomatosis of the gallbladder

	Segmental (n=12)	Generalized (n=10)	Fundal (n=8)
Male : female	6 : 6	7 : 3	3 : 5
Age (years, mean \pm SD)	52.0 \pm 9.3	48.9 \pm 15.6	55.8 \pm 10.3
Symptomatic patients	11 (92%)	10 (100%)	3 (38%)
With gallstones	12 (100%)	4 (40%)	4 (50%)
Cholesterol stones	6	1	3
Bilirubin stones	3	3	1
Other stones	3	0	0
Associated diseases other than gallstones	3	2	4
Abnormal P-B union	1		
Chronic hepatitis	1		1
Liver cirrhosis	1	1	1**
Duodenal diverticula			2
Gallbladder polyp		1	
Size of the affected portion (cm, mean \pm SD)	0.8 \pm 0.2*	1.2 \pm 0.6	1.7 \pm 0.5

* $p < 0.05$, ** associated with hepatocellular carcinoma, P-B; pancreatobiliary

Table 2 Preoperative diagnoses related to the types of adenomyomatosis and imaging techniques*

	Adenomyomatosis			Cholecystitis (n=15)	Benign polyp (n=5)	Cancer (n=3)
	Segmental (n=2)	Generalized (n=3)	Fundal (n=1)			
ERC	1	3	1	9	4	1
US	1	2	0	11	3	2
CT	1	1	0	5	0	1

* excluding one case of intraoperative determination, ERC; endoscopic retrograde cholangiography, US; ultrasonography and CT; computerized tomography

Table 3 Levels of carcinoembryonic antigen (CEA), CA19-9 and pancreatic secretory trypsin inhibitor (PSTI) in the gallbladder bile (mean \pm SD)

	CEA (ng/ml)	CA19-9 (U/ml)	PSTI (ng/ml)
Adenomyomatosis (n=8)	2.5 \pm 1.5*	77,900 \pm 36,900	115 \pm 53
Gallbladder cancer (n=6)	25.7 \pm 7.1	115,100 \pm 128,000	245 \pm 173

* $p < 0.01$

There was no postoperative mortality and morbidity related to a cholecystectomy. During the follow-up periods of 13 months to 8 years, one patient died of hepatocellular carcinoma, two died of extra-abdominal lesions, and three failed to complete follow-up. The remaining 24 patients are doing well in our outpatient division or according to the mail survey.

Discussion

Among the hypotheses on the development of AMG, the inflammation theory¹⁶⁾ had been abandoned because the hyperplastic mucosa in acalculus AMG seldom showed inflammatory changes^{4,28)}. Young patients were occasionally seen^{20,22,24)} in contrast to JUTRAS' theory¹²⁾ in which aging and its associated endocrine disorder might cause proliferative or degenerative changes in AMG. Some papillomatous or adenomatous epithelia of RAS may be seen, however, thickening of the muscular layer due to overgrowth of RAS obviously differs from neoplastic proliferation²²⁾.

To date, one theory in which excessive intraluminal pressure of the gallbladder plays a role in the development of AMG^{1,5,12)} may be plausible; when a portion of the mucosa is exposed to much higher pressure than normal, RAS already penetrating into the wall may begin to expand further and show diverticular or proliferative changes. Although this hypothesis is attractive, the changes of RAS in AMG principally remain within the wall in contrast to the extramural diverticula of the intestinal tract or urinary bladder^{6,22)}, and occasional papillomatous or adenomatous changes in the epithelia of RAS cannot be explained by simple mechanical pressure²²⁾. Thus, the pathogenesis of AMG is still unclear at present³⁾.

RAS appear at various incidences ranging from 34 to 93 percent of surgical specimens of the gallbladder⁹⁾. Although wall thickening due to proliferation of RAS is essential for AMG, the proposed criteria to distinguish AMG from only RAS-proliferation differ in details. We detected AMG using the above-mentioned guidelines²²⁾ in this survey, while, JUTRAS¹³⁾ defined AMG as that showing 3 to 5 times the thickened affected portion compared with the usual muscular layer. YAMAGIWA et al.³⁴⁾ described that the muscular layer should be more than 3 millimeters thick. MISONO et al.²⁰⁾ also stated that the thickened portion should be more than 3 millimeters with four or more coexistent RAS penetrating into the subserosa or deep muscular layer within one centimeter of the sample. Among the incidence of AMG in the resected specimens, differences ranging from 7 percent³⁴⁾ to 33 percent³³⁾ have been reported.

AMG is confined to adulthood²⁹⁾ except for sporadic cases of juvenile appearance^{20,24)}. In the English literature, females predominated over males ranging from a ratio of 1.7 : 1 to 3 : 1^{6,13,25)}. Above all, in the series of MEGUID et al.¹⁹⁾, all 32 patients were female. In contrast, including the present survey, no sex bias was proven in Japan^{9,20,22,23)} but two series showed that males predominated over females at a ratio of 1.8 : 1²¹⁾ or 2.1 : 1¹⁷⁾.

Although the pathohistology is quite different, from the clinical perspective, AMG and cholesterolosis can be viewed together¹⁸⁾. Although these conditions are capable of repeatedly causing abdominal pain and other symptoms, many patients whose gallbladders are affected by the conditions are entirely free of digestive complaints³⁾. If symptomatic, the chief complaints are pain³⁾ or vague indigestion¹⁹⁾. These symptoms are initially mild and transient, but with time, attacks become more frequent and intense and are often related to ingestion of fatty foods^{3,19)}.

In symptomatic patients with these changes, who also have gallstones, it is impossible to distinguish symptoms due to cholecystoses from those caused by calculi¹⁸⁾. MUTO²²⁾ reported a lower

incidence of colic in cases of acalculus AMG, however, some investigators^{9,24)} give different opinions. In clinical practice, AMG is highly coexistent with gallstones and the AMG-symptoms, per se, should be assessed in acalculus patients. In the present survey, typical colic was rare regardless of the presence of gallstones. Although vague complaints accounted for the majority of symptoms, patients who were affected by incidentally associated diseases other than gallstones showed more complicated signs and symptoms.

UCHIMURA et al.³³⁾ reported that S type of AMG was most frequently seen with an incidence of 44% out of 131 cases and that of G type was rare with the incidence of 12%. MISONO et al.²⁰⁾ also reported a similar tendency. However, MUTO²²⁾ noted 47 cases (43%) of F type and 40 cases (37%) of S type out of 109 patients. The incidence of S, G and F types in the present survey was 40, 33 and 27 percent, respectively. Although BEVAN⁴⁾ has suggested that the cause of pain in AMG-patients might be related to excessive neuromuscular activity of the hyperplastic gallbladder wall, the role of compartmentalization and abnormal gallbladder emptying in the occurrence of symptoms has not been established³⁾. To our knowledge, symptoms related to the types of AMG have seldom been documented. Although the number of instances in the present survey is small, patients with F type showed a tendency to be symptom free in contrast to patients of the other two types.

Physical findings in AMG are unremarkable. No laboratory data suggest the presence of AMG. If the cystic duct is patent, cholecystography is very useful for detecting AMG. In general, the gallbladder affected by AMG has JUTRAS' trias¹²⁾ indicating hyperconcentration, hyperexcitability and hyperexcretion by cholecystography. In typical cases, expanded and overgrown RAS are visualized very clearly in the contracting phase^{1,12)}. In any portion of the gallbladder, marginal appearance of RAS, that showing single or multiple and partial or diffuse shadow is demonstrated³⁾.

However, in consideration of a low incidence of RAS-opacification, which was approximately 5% on cholecystogram^{1,6,12)}, in clinical practice, possible AMG is detected mainly due to overall narrowing in G type, an hourglass deformity in S type and an elevated filling defect in F type¹⁾. Although TOMATSU³²⁾ suggested that ERC more clearly depicted RAS compared with excretory cholangiographies, MISONO et al.²⁰⁾ stated that the clearness of opacified RAS was no different between both techniques. ERC shows excellent visualization of the gallbladder lumen, however, the retrograde flow of contrast material through the cystic duct is occasionally disturbed.

On US of the abdomen, wall thickening of the gallbladder is usually seen in AMG as well as in other lesions. The expanded RAS showing multiple spots or minicysts with low echoic levels are characteristics of AMG^{10,26)}, however, they appear in approximately half of the cases¹⁰⁾. Occasional intramural high echoic levels are attributed to increments or stones in RAS or complex RAS themselves²⁶⁾. Although wall thickening of the gallbladder can also be seen on plain computerized tomography (CT), RAS depicted as a low density area have been reported in sporadic cases²⁷⁾. On CT following cholecystography, MISONO et al.²⁰⁾ and NAKADA et al.²⁴⁾ were able to observe RAS. Although selective arteriography¹⁰⁾ or laparoscopy^{4,21)} may be diagnostic for AMG, these techniques have seldom been employed except for suspected cases having a malignant lesion.

In the majority of patients, preoperative diagnosis of AMG was based on cholecystography^{3,9,19,20,22)}. In preoperative assessment in this survey, AMG was barely established before 1986, however, since then, six patients have been found with AMG before laparotomy by ERC and/or US. In clinical practice, AMG should be suspected in all patients showing wall thickening of the gallbladder. In the present survey, thirty patients with AMG accounted for 11.2% of 269 cases who were surgically observed as having wall thickening of the gallbladder by 3 millimeters or more.

Although gallstones do not predispose to AMG and the relationship between both conditions is still unknown at present, gallstones have been accepted to be only one factor having a significant incidence ranging from 13 to 84 percent^{6,12,22,23}) among coexistent diseases in AMG. In the present survey, twenty (67%) out of 30 patients with AMG had gallstones. These patients made up 3.1% of all the gallstone patients who underwent cholecystectomy during the duration of this survey, and 10 patients of acalculus AMG accounted for 4.1% of 242 acalculus patients during the same interval.

The tendency that AMG is observed more in specimens resected for cholelithiasis than in preoperative diagnosis by imaging techniques is pointed out^{22,23}). Although the incidence of coexistent gallstones was reported for more than 70% in each type of AMG^{22,33}), gallstones were accompanied in all patients of S type (100%), in 4 of F type (50%) and in 4 of G type (40%) in the present survey. Among the patients of calculus AMG, cholesterol stones accounted for 60% and bilirubin stones 25% showing a similar incidence obtained in usual cholelithiasis³³). So-called intramural stones formed in the expanded RAS are a well-known complication of AMG with an incidence as high as 49%²²). The incidence in our study was 20 percent.

AMG bears a close resemblance to some conditions including chronic cholecystitis in G type, congenital anomaly in S type, adenoma in F type, or carcinoma of the gallbladder in all types. Although some cases are associated with cholecystitis^{16,35}), the infected intracystic bile is rarely seen possibly due to the patent cystic duct. In the present survey, three patients of S type, two of G type and one of F type showed microbes in the bile, all were accompanied by gallstones.

The possibility of carcinoma should be ruled out than anything else. In the analysis of gallbladder bile, levels of CEA may become higher than normal in patients with gallbladder carcinoma³¹). YEATMAN *et al.*³⁶) also pointed out that significant elevation of CEA levels in patients suffering from colorectal metastases to the liver was noted. The significantly lower CEA levels of the gallbladder bile in the present cases of AMG compared to cases of gallbladder carcinoma may be suggestive of the non-neoplastic nature of AMG.

Generally, there was no problem of malignant transformation of AMG¹); however, a few cases involving carcinoma in the RAS-epithelia of AMG have been reported^{2,15}). SHIRAI³⁰) suggested that the carcinoma localized in the epithelia might be an early stage. Although we have never experienced such localized carcinoma in the RAS, carcinoma that not only resembles AMG but also localizes in the RAS should be kept in mind. In doubtful cases, specimens should be detected by intraoperative rapid pathology and permanent pathohistology.

Surgery is recommended for patients of AMG associated with gallstones whether they have symptoms or not. However, asymptomatic, acalculus patients are not candidates for surgery except for cases which are hard to distinguish from malignancy. Whether the gallbladder is functioning or not, symptoms of acalculus AMG due to possible hypercontraction of the gallbladder are easily ameliorated by simple cholecystectomy^{4,7,8,19,33}). Although in some cases of G type, dissection from the liver may be difficult, cholecystectomy is a common and safe procedure at present. However, gross examination of the entire mucosal surface and rapid pathology of the involved portion are mandatory. Final diagnosis of AMG depends on the histological findings. In addition, nine cases in the present survey were associated with liver cirrhosis, hepatocellular carcinoma, chronic hepatitis or other lesions, however, cholecystectomy showed no problems in postoperative course.

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和文抄録

胆嚢腺筋腫症：30手術例についての臨床的検討

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7年半の期間に胆嚢腺筋腫症30例を手術した。それらは同期間の胆嚢摘出手術を受けた896例の3.3%に相当し、3ミリメートル以上の胆嚢壁肥厚病変269例の11.2%を占めた。平均年齢は52.3歳、男女比8:7であった。術前に画像診断されたのは6例のみで、内視鏡的胆道造影や腹部超音波検査が特徴的な拡張 Rokitansky-Aschoff sinuses を証明するのに有効であった。腺

筋腫症の胆嚢胆汁中の carcinoembryonic antigen 値 (2.5 ± 1.5 ng/ml, mean \pm SD) は胆嚢癌症例に比べて有意に低かった ($p < 0.01$)。全症例に胆嚢摘出が容易に施行され、術後追跡してきた24例は元気である。胆石合併症例のみならず、無石症例でもなんらかの症状のある例、または悪性疾患疑診例に対しては、積極的な手術が必要と思われる。