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Adenomyomas of the Gallbladder

An Analysis of Frequency, Clinicopathologic Associations, and Relationship to Carcinoma of a Malformative Lesion

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• ***Context.***—**The nature and associations of gallbladder (GB) "adenomyoma" (AM) remain controversial. Some studies have attributed up to 26% of GB carcinoma to AMs.**

Objective.—**To examine the true frequency, clinicopathologic characteristics, and neoplastic changes in GB AM.**

Design.—**Cholecystectomy cohorts analyzed were 1953 consecutive cases, prospectively with specific attention to AM; 2347 consecutive archival cases; 203 totally embedded GBs; 207 GBs with carcinoma; and archival search of institutions for all cases diagnosed as AM.**

Results.—**Frequency of AM was 9.3% (19 of 203) in totally submitted cases but 3.3% (77 of 2347) in routinely sampled archival tissue. A total of 283 AMs were identified, with a female to male ratio = 1.9 (177:94) and mean size = 1.3 cm (range, 0.3–5.9). Most (96%, 203 of 210) were fundic, with formed nodular trabeculated submucosal thickening, and were difficult to appreciate from the mucosal surface. Four of 257 were multifocal (1.6%), and 3 of 257 (1.2%) were extensive ("adenomyomatosis"). Dilated glands (up to 14 mm), often radially converging to a point in the mucosa, were typical. Muscle was often minimal, confined to the upper segment. Nine of 225 (4%) revealed features of a duplication. No specific associations with inflammation, cholesterolosis, intestinal metaplasia, or thickening of the uninvolved GB wall were identified. Neoplastic change arising in AM was seen in 9.9% (28 of 283). Sixteen of 283 (5.6%) had mural intracholecystic neoplasm; 7 of 283 (2.5%) had flat-type high-grade dysplasia/carcinoma in situ. Thirteen of 283 cases had both AM and invasive carcinoma (4.6%), but in only 5 of 283 (1.8%), carcinoma was arising from AM (invasion was confined to AM, and dysplasia was predominantly in AM).**

Conclusions.—**AMs have all the features of a malformative developmental lesion, and may not show a significant muscle component; (ie, the name "adeno-myoma" is partly a misnomer). While most are innocuous, some pathologies may arise in AMs, including intracholecystic neoplasms, flat-type high-grade dysplasia or carcinoma in situ and invasive carcinoma (1.8%, 5 of 283). It is recommended that gross examination of GBs include serial slicing of the fundus for AM detection and total submission if one is found.**

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Adenomyoma (AM), also called "adenomyomatous hyperplasia" or "adenomyomatous nodule," has been noted as an often asymptomatic incidental lesion in cholecystectomies.[1,2] It is described as a collection of glands admixed with muscle, forming a small solitary mass. Some

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studies have found them to be commonly (≤89%) associated with cholecystitis and cholelithiasis.[3]

Even though AMs are not rare lesions, the data on their clinicopathologic associations are limited. The reported frequency in cholecystectomy specimens spans a very wide range from 0.8% to 33.3%.[4–6] The nature of AMs is also controversial; some authors believe that AMs are acquired lesions that are merely an exaggerated or localized form of Rokitansky-Aschoff sinuses due to chronic injury. In fact, AM was initially described by King and MacCallum in 1931 as "cholecystitis glandularis proliferans (cystica)."[7] Others maintain that AMs are congenital rests as these lesions can be seen even in childhood.[8–10]

The association between AM and carcinoma has been a subject of much debate. The predominant view is that AM is an insignificant finding,[2,11] only very rarely and incidentally showing dysplastic epithelium represented as rare case reports.[12–14] We recently described AM as a source of a distinctive tumoral intraepithelial neoplasm,[15,16] mural intracholecystic neoplasm (ICN),[1] which is akin to a mass-forming preinvasive neoplasm in the pancreatobiliary region, especially branch-duct type intraductal papillary mucinous neoplasm (IPMN). These neoplasms, however, overall, appear to be rare occurrences. In contrast, some studies have claimed that the prevalence of gallbladder carcinoma (GBC) is higher in adenomyomatous gallbladders (GBs).[17,18] In fact, in a recent study by Kai et al, 26% of GBCs were thought to be arising in association with an AM.[17]

The aim of this study was to investigate the true frequency of GB AM and to document its clinicopathologic associations with the goal of further clarifying its nature, assess its significance, and determine its association with neoplastic changes in the GB.

MATERIALS AND METHODS

Case Identification

Cases were identified from 5 different cohorts.

In the first cohort, 1953 consecutive cholecystectomy specimens from University of Health Sciences Istanbul Training and Research Hospital, Istanbul, Turkey, included regardless of the cause of cholecystectomy, were prospectively subjected to gross examination with emphasis on searching for AM and to determine its frequency.

As a separate cohort, 203 cholecystectomy specimens from the United States were submitted entirely for microscopic examination according to a protocol, in order to establish the relative frequencies of various pathologic findings. In the cases examined per this protocol,[19] the first section was obtained to represent the "random" section, which involved a full slice of the GB wall from fundus to neck on the antihepatic center of the GB. Then, the rest of the GB was submitted in toto.

Separately, 2347 archival cholecystectomy specimens in the institutional files of Wayne State University (Detroit, Michigan) and Emory University (Atlanta, Georgia) that had been sampled routinely were retrieved and histopathologically reviewed to identify the AMs.

In order to identify the AM cases not captured in the cohorts above, a computer search was performed to identify all cases designated as "adenomyoma" and "adenomyomatous" in the GB in the archival pathology files of Wayne State University and Emory University. Cases identified that had not been already captured in the other cohorts were also retrieved and included in the analysis for overall clinicopathologic characteristics of AM.

Additionally, 207 cholecystectomies with primary GB invasive carcinoma in the files of Wayne State University and Emory University were re-reviewed specifically for the presence of an underlying AM and any association of AM with carcinoma.

In all these cohorts, cholecystectomy indication (the reason for cholecystectomy) was disregarded and even GBs removed during transplants and other operations such as pancreatoduodenectomy were also included.

Pathological Analysis

Microscopically, the collection of cystically dilated glands forming a small solitary mass or a band of trabeculated thickening of the GB wall with sieve-like configuration were defined as AM. The localization, multifocality, and involved field were recorded. The presence of muscle, presence of hypercellular stroma, muscle localization (base or superficial), largest cyst diameter, contours of the cysts, and connection to the surface epithelium were noted. All the identified cases were reviewed by one of the pathologists (N.V.A.) for inclusion in the study.

Also examined was the presence of associated pathologies: cholesterolosis and the signs of injury such as acute and chronic inflammation, the presence of Rokitansky-Aschoff sinuses, pyloric metaplasia, and intestinal metaplasia. The average thickness of the uninvolved GB segment was measured. These histopathologic findings were also analyzed in 290 cases randomly selected among 1953 consecutive routinely sampled cholecystectomy specimens without any AM, which served as the control group. The basic principles used in sampling applied in these cases were later published in a review article.[20]

The dysplastic and carcinomatous changes were investigated and typed according to the World Heath Organization 2019 and other updated criteria.[1,15,20,21]

Statistical Analysis

All results were presented as mean and standard deviation for continuous variables and as number and percentage for categorical variables. Normality of numerical variables was tested by the Kolmogorov-Smirnov test. Numerical data with normal distribution were analyzed by an independent samples *t* test; data with skewed distribution were analyzed by a Mann-Whitney *U* test. Categorical variables were presented as percentages and analyzed by a χ^2 test. The 1-way analysis of variance (ANOVA) was used to determine any statistically significant differences among more than 2 independent (unrelated) groups for normal distribution. A Kruskal-Wallis test was used to describe for abnormal distribution. One-way ANOVA and a Kruskal-Wallis test were used to assess for significant differences on a continuous dependent variable by a categorical independent variable for more than 2 groups (normal and abnormal distribution, respectively). A Tukey test was used to compare the differences between the parametric variables. A Dwass-Steel-Critchlow-Fligner test was used to compare the differences between the nonparametric variables for differences between the groups. A Pearson χ^2 test was used to compare the differences between categorical variables. Pearson (normal distribution) and Spearman (abnormal distribution) correlation analyses were used to evaluate the relationship between variables.

All the statistical analyses were performed by using Jamovi project (version 0.9) computer software.[22] $P < .05$ determined statistical significance.[20–23]

RESULTS

Frequency

In the cohort that was specifically grossly examined and investigated for AM, the frequency was 6.9% (135 of 1953). In the cohort that was submitted entirely for microscopic examination, 9.3% (19 of 203) revealed AM; however, some of these were fairly small. In the archival cholecystectomy specimens, this figure was 3.3% (77 of 2347). Other cohorts including personal consultations and cholecystectomies with primary GB invasive carcinoma revealed 52 additional AM cases.

Clinicopathologic Characteristics of Adenomyomas in Comparison With Other Conditions in the Gallbladder					
	Adenomyomas (n = 283)	Chronic Cholecystitis (n = 483)	Dysplastic Gallbladder (n = 199)	Gallbladder Carcinoma (n = 427)	*P* Value
Mean age, y	56	49	57	64	$P = .75$
Female to male ratio	1.9 (177:94)	2.6 (349:134)	3.6 (156:43)	4.1 (344:/83)	$P < .001$
Pyloric metaplasia, %	26 (52 of 197)	38 (183 of 483)	80 (159 of 199)	51 (216 of 427)	$P < .001$
Intestinal metaplasia, %	4.1 (8 of 197)	11 (53 of 483)	50 (100 of 199)	26 (111 of 427)	$P < .001$

Clinicopathologic Associations

A total of 283 AMs were identified from the different cohorts searched, and the clinicopathologic analysis of all of them together revealed the following findings.

Clinical Findings.—The female predominance characteristic of GB pathologies was not as striking in AMs: the female to male ratio was 1.9 (177:94), as opposed to ordinary cholecystitis, where the ratio was 2.6, or invasive adenocarcinoma, which was 4.1 in the same cohorts analyzed. The mean age at which AMs were discovered in cholecystectomies was 56 years (21–95 years) (Table), slightly older than patients in the ordinary cholecystitis cohort (mean, 49 years), but younger than carcinomas (mean, 64 years).

Macroscopic Findings.—Most AMs were localized and solitary (97.3%, 258 of 265 with available information) and 96.6% (203 of 210 with available information) of them were exclusively fundic (Figure 1, A through C), only 2 were localized in neck and 1 in the corpus. Multifocality or diffuse involvement (Figure 1, D) was extremely rare (2.7%, 257 with available information), with diffuse involvement seen in only 3 cases. The localization information of 74 cases was missing. The mean size of AMs was 1.3 cm (range, 0.3–5.9 cm).

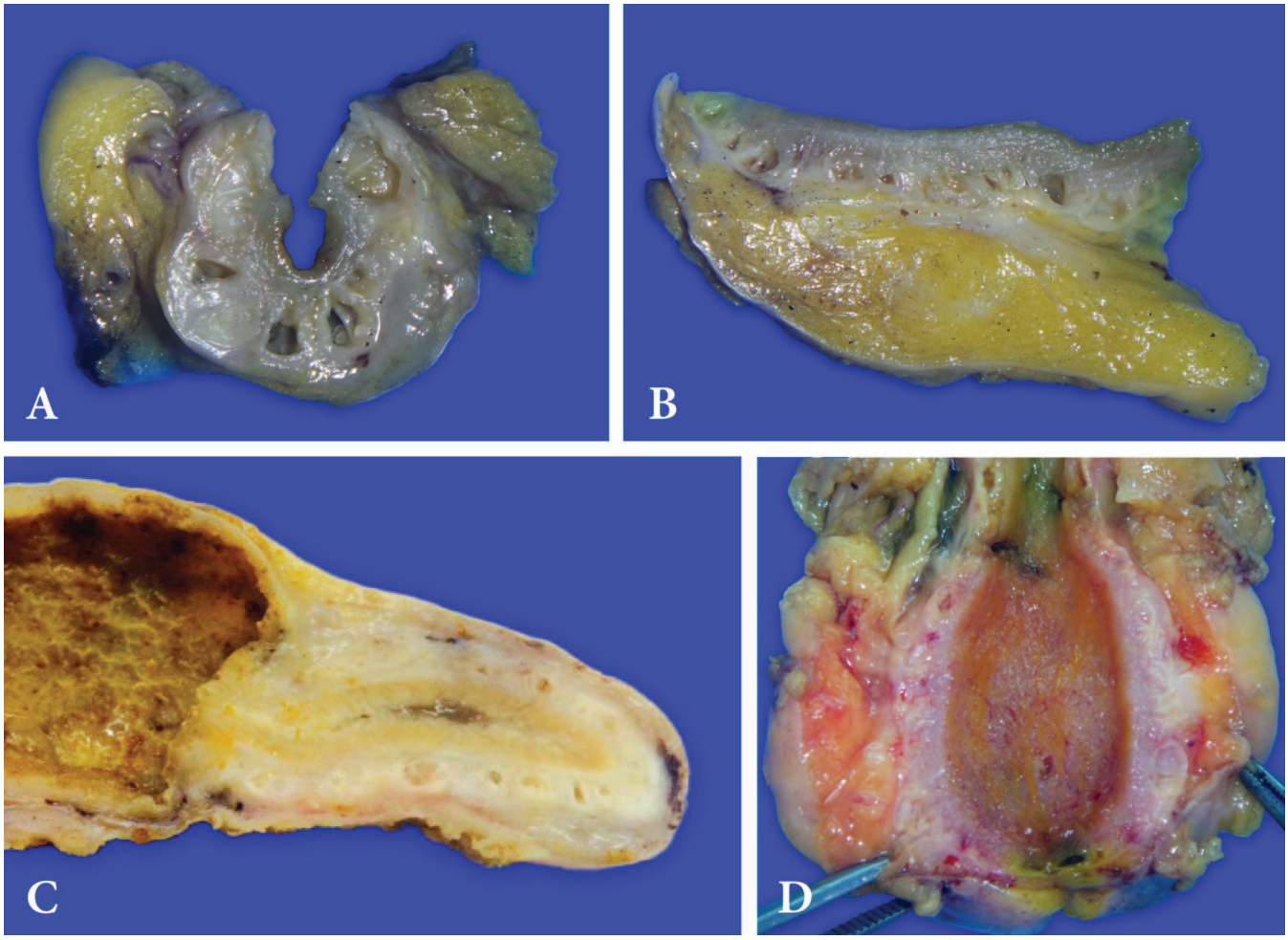

Figure 1. *Adenomyoma, distribution. Most adenomyomas are localized lesions that form nodules on the wall that are covered by mucosa and may not even be noticeable from the mucosal perspective. Many are round structures that appear to converge at a focus in the mucosa centrifugally, forming a reverse cup-shaped structure (A). Another common presentation is the plaquelike thickening of the gallbladder wall with the cut sections showing trabeculations due to the cystic glands intervened by hypertrophic stroma (B). In some adenomyomas there appears to be an occluded lumen in the center that closely resembles a duplication (C). Diffuse examples are much less common and typically appear as thickened wall with prominent trabeculations (D).*

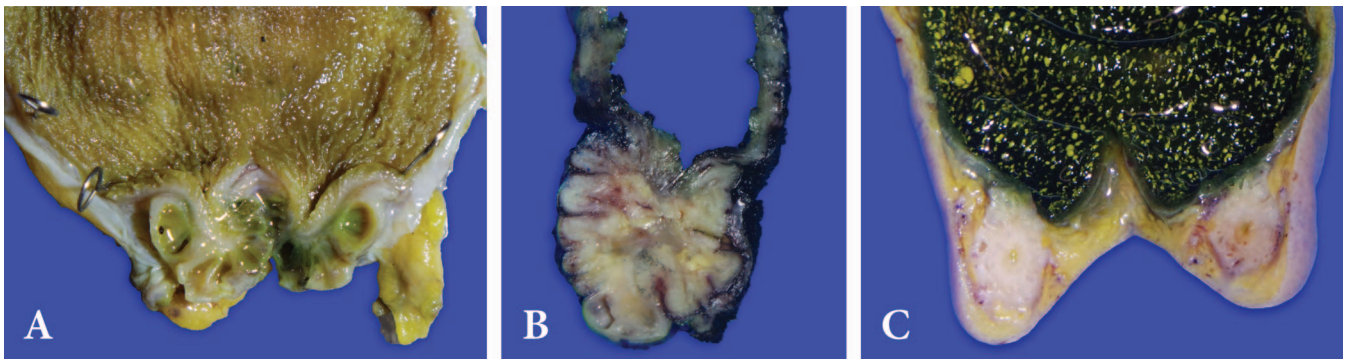

Figure 2. *Adenomyoma, spectrum of cystic and solid components macroscopically. In addition to the characteristic trabecular architecture that is the most common pattern (see Figure 1), adenomyomas also show a spectrum of cystic structures. Some appear like a submucosal multilocular cystic lesion (A), some as multinodular lesion with focal cystic change (B), and some others as an almost entirely solid nodule (C). Cystic structures may be impacted with bile and may occasionally reveal calculi (not shown).*

Macroscopically, AMs were often unrecognizable from the mucosal perspective other than forming a subtle elevation (depending on how the sample was placed on the table). In many cases a subtle dimple could be appreciated (Figure 1, A, and Figure 2, A and B). Of the 19 AMs that were identified in the cohort of 203 cases that were entirely submitted for microscopic examination, only 1 of 203 (0.5%) was detected in the "random" section of the protocol, the remaining 18 were found in the other sections.

On cut sections, AMs could be distinguished from the rest of the GB wall as a cup-shaped nodule or a zone of trabeculation or thickening (Figure 1, A through D, and Figure 2, A through C). Sievelike multicystic appearance was observed in 98% of the cases (276 of 283) and 7 of 283 cases (2.4%) showed seemingly unilocular cyst formation. Some did not show overt cyst formation in macroscopic examination but exhibited the characteristic trabecular appearance (Figure 1, C, and Figure 2, B and C).

The mean thickness of the uninvolved GB wall was 3.6 mm in cases with AM versus 3.3 mm in the controls. Gall stones were present in 113 of 228 (49.5%) cases with available information. Occasionally the nodule appeared more solid (Figure 2, C).

Microscopic Findings.—On low power, AMs showed a conglomeration of dilated glands (Figure 3, A), up to 14 mm. The surface was typically intact and normal appearing but formed a dimple (Figure 3, A and B). Glands and cysts appeared to be radially converging to the dimple in the mucosa (Figure 3, A, and Figure 4, A and C), but not individually opening to the surface (Figure 3, A and B, and Figure 5, A and B). In many cases, depending on the section taken, the lesion appeared to have a central muscle-coated structure in a fashion seen in a true diverticulum/duplication (Figure 3, A, and Figure 4, A through C). In 9 of 283 cases (3.1%), this appeared to be a separate, independent miniature GB on the wall (Figure 4, A through C) with a complete muscular wall. The cystic glands typically revealed irregular contours, and this was striking in 42 of 283 (14.8%) cases.

Muscle component was highly variable, and in 95 of 283 (33.5%) cases no discernible muscular proliferation other than the ordinary tunica muscularis could be identified. The muscular component, if present, was more prominent around the superficial aspect of the lesion or was dense at the center (Figure 3, A through C, and Figure 6); this characteristic appeared to be more prominent in those that

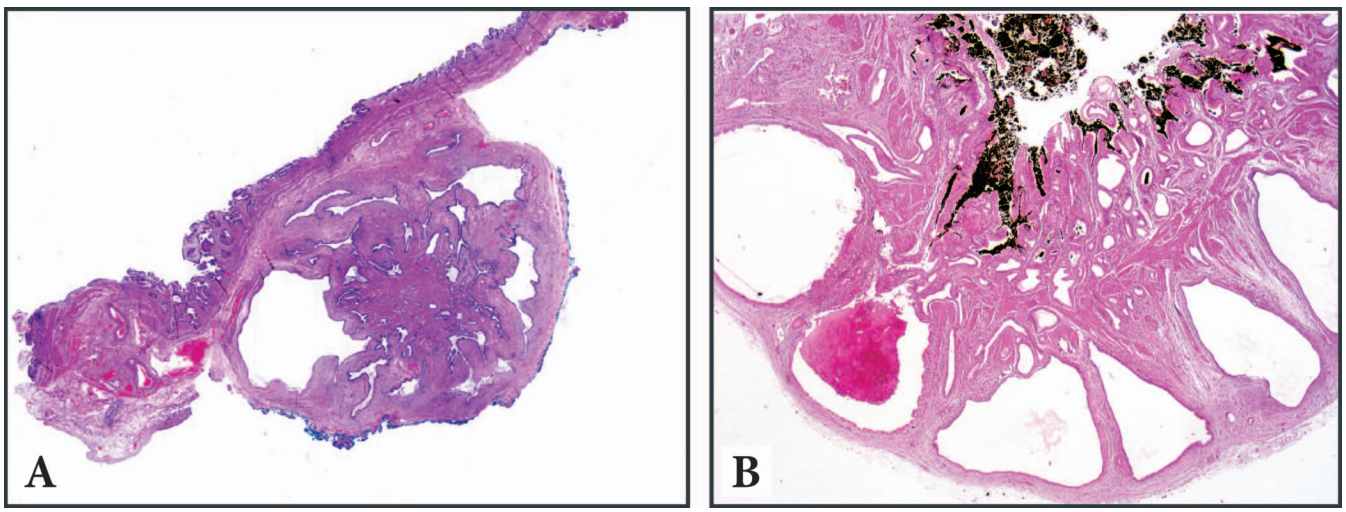

Figure 3. *Centrifugal pattern of adenomyoma. Most adenomyomas have a round flasklike configuration with more cystic structures at the periphery appearing to point toward a central focus in the surface gallbladder mucosa, which may show a subtle dimple (A) or a slight invagination (B) at that location (hematoxylin-eosin, original magnifications ×10 [A] and ×100 [B]).*

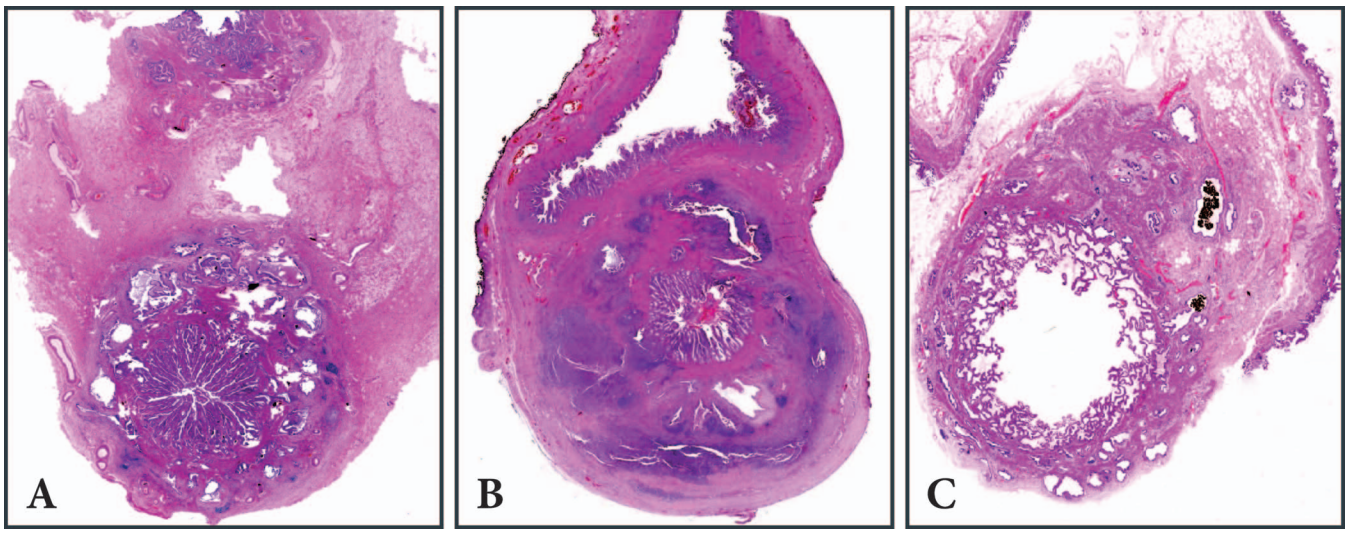

Figure 4. *In some adenomyomas, presumably also related to the plane of sectioning, the convergence phenomenon illustrated in Figure 3 is not evident, and instead the whole lesion appears as a separate gallbladder with a well-formed wall and layering (hematoxylin-eosin, original magnification ×10 [A, B, and C]).*

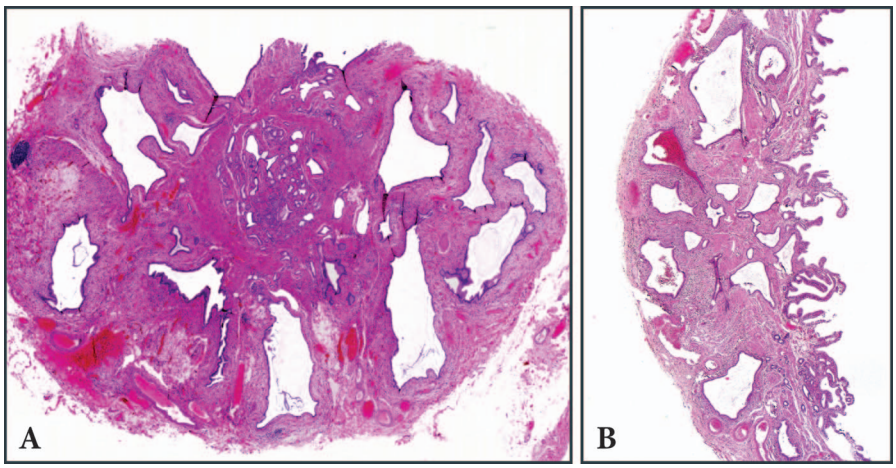

Figure 5. *In most adenomyomas, the glands or cysts tend to be larger at the periphery (also illustrated in Figure 3), and they often display substantially irregular contours. This zonation phenomenon is more striking in the rounder examples in which the muscle is also more abundant centrally (A). In those with more plaque-like growth (B), this zonation phenomeonon is not as evident (hematoxylin-eosin, original magnification ×10 [A and B]).*

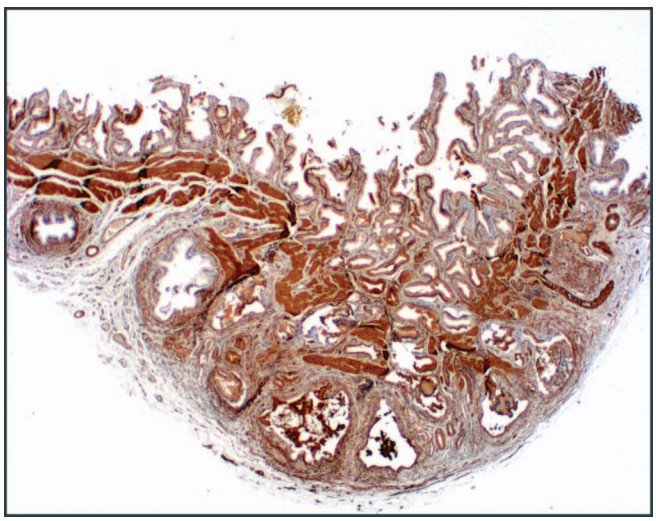

Figure 6. *This actin stain shows the variable muscle distribution in adenomyomas. The tunica muscularis of the native gallbladder is somewhat disrupted in the area of adenomyoma. In the lesion itself, the muscle is more condensed in the central and superficial segments and decreases toward the serosa (actin, original magnification ×10).*

were captured tangentially (rather than perpendicular to the mucosa). In fact, it looked like the muscle was thicker and more abundant in the neck of an infundibular-shaped structure (Figure 3, A and B, and Figure 6). On the other hand, in cases that appeared like a duplication and were sectioned with the lumen at the center, a continuous muscle band surrounded the central mucosa (Figure 4, C).

In some examples, the stroma around the cystic glands had mild cellularity of spindle cells. Occasionally, this, combined with the mucinous change in the epithelium, created a picture reminiscent of the ovarian stroma of mucinous cystic neoplasm (Figure 7, A and B).

Pathologic Associations.—The surface epithelium was typically intact and unremarkable in 75% (193 of 257 with available information) of the cases. There was no specific association with other types of injury in the GB. The mean thickness of the uninvolved GB wall was 3.6 mm in GBs with AM versus 3.3 mm in those without (control group). Cholesterolosis was present in 76 of 283 cases (27%). Stones were recorded in 49.5% (113 of 228); however, the gallstone frequency was not reliable because in many cases the stones had been removed and given to the patient's family without proper recording. Acute cholecystitis changes (edema, tissue

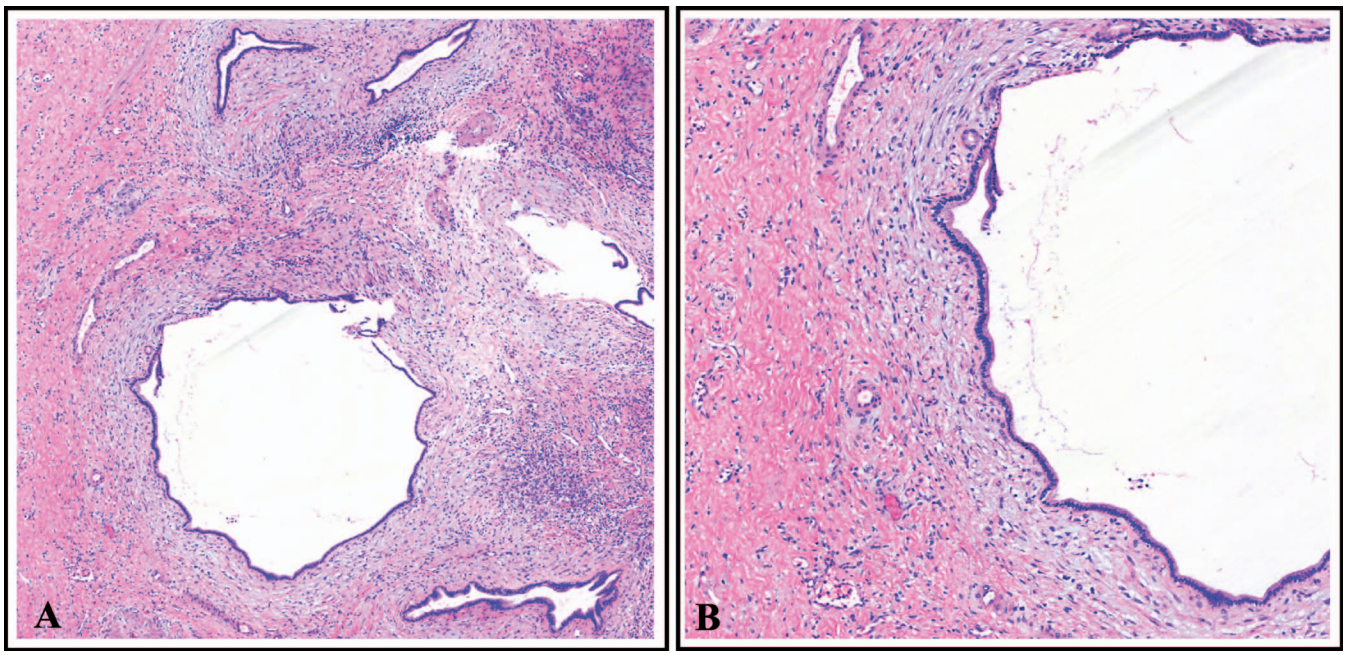

Figure 7. *Peculiar stromal changes often accompany the glands of adenomyomas. Taken in isolation, this can be interpreted as "desmoplastic" stroma of an invasive process. In some cases the stroma adjacent to the glands or cysts is more cellular, creating a picture that has been misinterpreted as ovarian stroma of mucinous cystic neoplasm (hematoxylin-eosin, original magnifications ×10 [A] and ×40 [B]).*

culture fibroblast, ulceration, hemorrhage) was seen almost exclusively in the AM of 3 of 283 cases (1%). Chronic inflammation and fibrotic changes were seen in 141 of 283 cases (50%) and were mostly mild.

Pyloric gland metaplasia was even less common in the uninvolved mucosa of the GB than controls (26% versus 38%, $P < .001$) (Table). Intestinal metaplasia (goblet cells) was also less frequent both in the AM itself, noted in only 4.1% (8 of 197) (as opposed to 10.9% [53 of 483] in control, $P < .001$), as well as in the uninvolved GB of AM cases, seen in only 8 of 283 cases (2.8%).

Neoplastic Changes in Adenomyoma

Overall neoplastic change that appeared to be arising in AM was seen in 28 of 283 cases (9.9%). Sixteen of 283 (5.6%) had mural ICN, which was the subject of a separate study.[1] To mention this here briefly as it pertains to this study, these were cystic papillary and mucinous tumoral intrapithelial neoplasms akin to branch-duct IPMNs of the pancreas, seen in elder patients (mean age 68 years) and slightly larger than ordinary AMs (1.7 cm). Unlike other GB lesions, these were slightly more common in men (female to male ratio = 0.8). Three of the cases had high-grade dysplasia or carcinoma in situ (CIS) and 2 had invasive carcinomas that were small, 0.2 and 0.8 cm, respectively.

Separately, in this current study 7 of 283 cases (2.5%) had flat-type high-grade dysplasia or CIS in the AM epithelium at microscopic examination (without florid papillary nodule formation). In these 7 cases there was no dysplasia in the uninvolved mucosa.

Overall, in 13 of 283 cases there were both identifiable AM and invasive carcinoma. In 5 of these (1.8%), the invasive carcinoma was clearly arising from AM (Figure 8), with the invasion confined to the AM area, measuring 0.1–0.9 cm, and the dysplasia was exclusively or predominantly in the AM as well. Only 1 of these had dysplastic changes in the native GB mucosa outside of AM. The median number of blocks examined in these 5 cases was 15 (range, 6–27), and 3 of these were recorded to have total sampling. In the remaining 8 cases with concomitant AM and invasive carcinoma, 2 had invasion involving both AM and the uninvolved GB (thus it was difficult to establish a causal or spatial assocation with AM), and in 6 cases, invasive foci were away from the AM, although the AM also had dysplasia or CIS.

In terms of staging, all 5 AM-associated invasive carcinomas were located on the wall of the AM and were spatially beyond the tunica muscularis, and as such they had

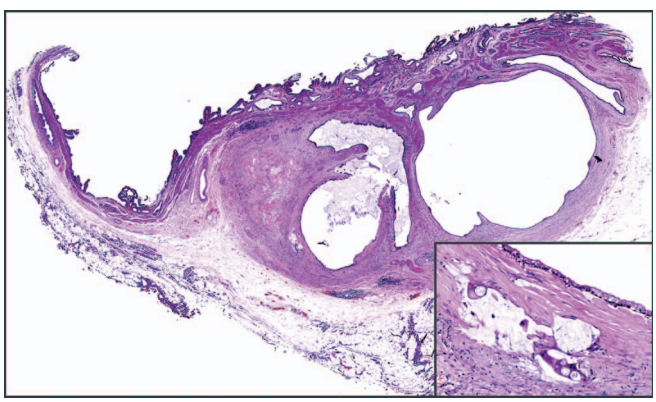

Figure 8. *Microscopic invasion in adenomyoma (AM). The lesion in the figure has the characteristic features of AM as illustrated in Figures 1 through 6 including the zonal muscle distribution, dimple-like structure on the surface mucosa corresponding to the middle of the lesion, and dilated glands forming a mural nodule. In this AM, there was a microscopic focus of invasive carcinoma (inset) in addition to dysplastic changes in the glands of the AM. Although the invasion is very small, it had to be qualified as T2 just by default of its localization (hematoxylin-eosin, original magnifications ×10, inset ×400).*

to be qualified as T2, although they were very limited in amount as described above (Figure 8). All 5 of these cases had survival information. The median follow-up of the cases is 37 months (6–122 months) and a patient with a 3-mm invasion was alive after 10 years. One patient died due to the metastatic disease 37 months later. One of the patients died within a month due to surgical complications (perioperative mortality).

DISCUSSION

Frequency

In the literature, the reported frequency of AM has a wide range from 0.6% to 33%.[4,6,18,24,25] This variation is attributable partly to the recognition phenomenon (including sampling and reporting), and partly to the diagnostic criteria and AM's distinction from Rokitansky-Aschoff sinuses, which occur in more than half of injured GBs. In this study, in order to establish the frequency of AM, 1953 consecutive GBs were examined prospectively, and its frequency was established as 6.9% (135 of 1953) in this particular cohort. In the cohort in which the GB was submitted in total, this figure was 9% (19 of 203), but several of these AMs were fairly small. In contrast, in the archival material that had been evaluated in routine diagnostic workup, the frequency was 3.3% (77 of 2347), which confirms that the sampling-recognition phenomenon is at play. As elucidated in this study, AM is typically covered by mucosa, and the GB is often unremarkable, and therefore, unless thorough slicing is performed, AM, which has median size of 1.3 cm, is often missed. Of note, only 1 of the 19 AM cases in the total submission cohort of 203 cases had the AM discovered in the initial ("random") section (0.5%). This confirms that unless the fundus is dissected thoroughly, AM may not appear in the sections submitted for microscopic examination. Moreover, unless gross microscopic correlation is performed or the pathologists are aware of the distinctive characteristics of AMs, they can be easily dismissed as Rokitansky-Aschoff sinuses in routine microscopic examination. Conversely, Rokitansky-Aschoff sinuses are also misdiagnosed as AM when they are clustered and accompanied by muscular hypertrophy. Studies that have conducted purposeful examination of GBs and used the conventional criteria typically record a frequency similar to ours.[6,24] For practical purposes, we can state that, in routine diagnostic workup, AM is discoverable in about 6.9% (135 of 1953) of GBs by proper slicing of the fundus and selective sampling.

Nature and Cause of AM

All the findings in this study point to a developmental malformative nature of AM. AM had originally been described as "cholecystitis glandularis proliferans (cystica)" by King and MacCallum in 1931.[7] Subsequently, several studies also attributed AM to chronic injury.[7,26] Later, the occurrence of AM in infants and children challenged this view.[27–30] Our study further clarifies that AM is not a product of injury. In this study, most AMs were not associated with any inflammatory fibrotic process in that particular location or elsewhere in the GB. Instead, the fundus is the region where embryologically ductular processes are clustered. Moreover, some AMs acquire the appearance of a GB duplication (Figure 4, A and C), forming a distinct round structure with a complete muscular coat and central mucosa, which was very prominent in 3.1% (9 of 283) of the cases in this study. All these findings point toward AM being a developmental malformative process.

Adenomyoma Term Is Partly a Misnomer

Although this process has been called adeno*myo*ma, the muscular component is highly variable, and in fact, is minimal in many cases. For the examples that are more flask-shaped in the sections, the muscle is typically toward the neck of the flask and tends to disappear in the more dilated, deeper aspects of the glands or cysts. On the other hand, for those cases that appear to be duplication, there is a continuous well-formed muscular coat that surrounds the central mucosa with more glands at the periphery.

The "-oma" suffix may also be misleading. This study establishes that AM is not a neoplastic process, although occasionally neoplastic change can occur in them. The term adenomyomatous "hyperplasia" has also been used in the literature but AMs do not appear to have a hyperplastic nature. The findings here confirm that AM does not appear to be either a secondary (injury induced) or primary form of hyperplasia. It does not appear to be a pressure-related localized phenomenon because there often is no association with stones, or any sign of pressure or any injurious agent in the GB. Clonality analysis may nevertheless be interesting to perform in AMs.

Clinicopathologic Characteristics

AM does not seem to have a striking female to male ratio predilection. It occurs almost exclusively in the fundus, to an extent that it is justifiable to refer to it as "fundic adenomyoma," such that a lesion elsewhere is very unlikely to be AM. Most are localized, although more segmental and diffuse forms can be encountered, albeit very rarely. They tend to be relatively small with a mean size of 1.3 cm and are seldom larger than 2 cm. Diffuse and segmental examples are larger. AMs are often unrecognizable from the mucosal perspective and missed in random sections. A gross finding of trabeculation on the wall or a mural nodule formation with microcysts is diagnostic. This correlates nicely with the microscopic findings of a conglomerate of cystic glands forming a band or a relatively well-outlined nodule. One often gets the impression that these glands are centrifugally pointing toward a single focus rather than each individually opening to the mucosa themselves. Muscular participation is highly variable, and often minimal to none. Some examples form a distinct duplication-like nodule with all the features of a miniature GB on the wall. Occasionally, stroma shows a subtle hypercellularity that creates a pattern reminiscent of mucinous cystic neoplasms (with ovarian stroma).

AM is usually discovered in GBs without any significant injury, although of course it can be detected in GBs removed for acute and chronic cholecystitis as well and show inflammation and injury. Occasionally inflammation can be confined to the AM and not seen in the remainder of GB, but this is uncommon. AM epithelium often has a mucinous tinge to it, rather than having the acidophilic cytoplasm more typical of the mucosa of GB proper. Of note, pyloric gland metaplasia and intestinal metaplasia, which are regarded as signs of injury, were not any higher in the GBs with AM than other cohorts analyzed, and in fact, were observed even less frequently in the cases with AM in this study. However, this lower frequency may be a reflection of a case selection bias in different cohorts. Nevertheless, we

have not found any evidence of injury playing a role in the development of AMs in these patients.

AM as a Source of Neoplasm

The literature has a greatly variable impression regarding the association of AM with neoplastic transformation. There are several case reports of dysplastic changes in the AM. We recently reported the clinicopathologic findings of a series of ICNs arising in AMs,[1] which formed tumors akin to branch-duct IPMNs of the pancreas. Not surprisingly, AMs can generate dysplastic transformation. However, it has been controversial as to how often this occurs. In the study by Kai et al,[17] AM was thought to be the culprit in 26% of GBCs. In our study, neoplastic change was found in almost 10% (28 of 283) of the AMs, and only 1.8% (5 of 283) had invasive carcinoma. For this purpose, we also reviewed our GBC database (207 cases with invasive carcinoma) for the specific association with AM and could not demonstrate a significant number. However, it should be acknowledged here that our GBC database consists of archival material that had been sampled without any specific protocol. It is possible that in some of the cases the association with AM had been missed (not properly sampled) and, on top of that, it is plausible that by the time invasive cancers came to clinical attention, the underlying AM had already been destroyed and was unrecognizable. This issue needs further investigation. At the time being, our recommendation is that the fundic region of every GB specimen is sliced and examined thoroughly in the gross pathology room for the presence of AM and if one is discovered, it should be submitted entirely for microscopic examination, which is typically 1 cassette.

One issue about the invasive carcinomas arising in AM is the applicability of current TNM staging for such cases. In this study, all 5 invasive carcinomas that were clearly arising from the AM were in the peri-muscular level (from the GB proper perspective) and as such qualified as pT2 carcinoma. pT2 GBCs are regarded aggressive malignancies with a 5-year survival of about 45%.[31] However, these invasive carcinomas arising in AMs were also fairly small (0.1–0.9 cm), and emerging data indicate that minimal or superficial GBCs may behave like in-situ carcinoma.[32,33] On the other hand, invasive carcinomas that extend to within 1 mm of external surfaces are prone to spread and have a dismal prognosis.[34] For these reasons, at the time being, we recommend reporting both the size and the distance of the invasion from the external surfaces, with a comment.

Management Implications

The fact that 9.9% (28 of 283) of AMs proved to have neoplastic changes brings up an important and challenging management question. Perhaps, extrapolations from incidental pancreatic cysts, which are similarly seen in 5% to 15% of the general population, may be helpful in this regard. For the cases with ICN (adenomatous papillary nodules) arising in an AM, indeed the analogy with branch-duct IPMNs is highly applicable, since both entities show invasion in about 15% (almost identical figure in both).[1] It is presumed that the papillary nodules that develop in and characterize these AM- ICNs are likely to be visible as "mural nodules" at the radiologic level, although we do not have data on this yet. It is also possible that these AM-ICNs may show some growth in follow-up (hopefully before they invade) but this is also not known at this time.

Those incidental (and typically small) in situ or invasive carcinomas without an adenomatous component, which were found in about 7% (20 of 283) of the AMs in this study, raises a much bigger management concern. Since these are ordinary carcinomas, it is safe to assume they would have behaved aggressively if they had not been removed. By nature, these are very unlikely to show any radiologic manifestation, considering they are underwhelming even to naked-eye observation. It is difficult to determine at this time whether it is justified to remove them all.

All in all, although it is difficult to create a specific management protocol for AMs at this time, it is clear that they need to be examined more carefully than previously thought. In examining a cholecystectomy specimen in the gross pathology room, slicing of the fundus even in seemingly normal mucosa (which the surface of AM typically shows), is warranted. The difference in the frequency elucidated in the totally embedded GBs (9.3%; 19 of 203) versus the randomly sampled archival material (3.3%; 77 of 2347) suggests that some AMs may be being missed in routine examination. Considering that incidental high-grade dysplasia can occur (albeit in a small percentage), even in small AMs, their examination is warranted. For AMs discovered incidentally in radiologic examination with otherwise no indication for cholecystectomy, the question becomes more challenging. Such cases may perhaps have to be subjected to more detailed radiologic analysis, at least to establish the baseline findings, so that if the patient receives other radiologic tests in the future, a change in its characteristics can be evaluated. Considering carcinomatous transformation is detected in less than 4.6% (13 of 283) AMs, this degree of risk may not necessarily justify a specific surveillance protocol in an otherwise innocuous AM without any signs of AM-ICN or other abnormalities. However, naturally, more studies are needed in this regard.

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