Adenomyomatosis Concomitant with Primary Gallbladder Carcinoma

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Some clinicians have proposed a relationship between gallbladder (GB) cancer and adenomyomatosis (ADM) of the gallbladder, although the latter condition is not considered to have malignant potential. We retrospectively reviewed the surgical pathology database of patients who underwent resection for ADM of the gallbladder at our institution from March 2005 to May 2015. In total, 624 patients underwent surgical resection of the gallbladder with Rokitansky-Aschoff sinuses. Of these cases, 93 were pathologically diagnosed with ADM of the gallbladder, with 44 (47.3%) classified macroscopically as fundal-type ADM, 26 (28.0%) as segmental type, and 23 (24.7%) as diffuse-type ADM. In 3 of the 93 (3.2%) resected specimens, early-stage GB carcinoma was detected, although preoperative imaging did not suggest a malignant neoplasm of the gallbladder in any of these patients. GB cancer subsequently developed in the mucosa of the fundal compartment distal to the annular stricture of the segmental-type ADM in 2 of these patients and against the background of the fundal-type ADM in 1 patient. This study revealed the difficulty of early diagnosis of primary GB cancer in the setting of concurrent ADM, and clinicians should be aware of this frequent coexistence.

Key words: adenomyomatosis, gallbladder carcinoma, Rokitansky-Aschoff sinuses, surgery, carcinogenesis

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cal pathology database of Kochi Health Sciences Center to identify patients who underwent resection for ADM of the gallbladder in the roughly 10-year periods from March 2005 to May 2015. All diagnoses of ADM of the gallbladder and GB carcinoma were confirmed by pathological analysis.

**Assessment.** Using the original surgical specimens, 2 expert pathologists (J.I. and M.M.) at our hospital confirmed the location of both ADM of the gallbladder and the GB cancer, including the size of the tumor, its stage, the degree of differentiation, vascular invasion, lymphatic permeation, perineural invasion, retroperitoneal invasion, and lymph node metastasis. We investigated and revisited whether there was a relationship between ADM of the gallbladder and GB cancer and whether ADM of the gallbladder is a risk factor for GB cancer by de novo sequence.

**Results**

**Patients.** We analyzed the cases of 624 GB with RAS who underwent a surgical resection. We found that 509 of the patients had clinical symptoms due to cholecystitis, in 14 patients a cholecystectomy was performed with gastrectomy, in 13 patients with pancreatocoduodenectomy, in 13 with surgical management for peritonitis induced by perforation of gastrointestinal tracts, in 11 with liver resection, in 11 with carcinoma of GB, in 6 patients with colectomy, in 5 with esophagectomy, in 2 with splenectomy, and in 40 patients with RAS did not show any clinical symptoms.

Among the 509 patients who suffered from cholecystitis, 397 patients had gallbladder stone, and of these 397 patients, 93 were pathologically diagnosed with ADM of the gallbladder: 44 (47.3%) were macroscopically classified as the fundal type, 26 (28.0%) as the segmental type, and 23 (24.7%) as the diffuse type. The 93 patients with ADM of the gallbladder (48 men and 45 women) ranged in age from 29 to 98 years (mean 58.0 years).

GB carcinoma was detected pathologically in only 3 of the 93 resected specimens (3.2%). Table 1 details the characteristics of the patients analyzed in this study.

**Clinicopathological findings.** Table 2 describes the clinicopathological features of the 3 surgical specimens showing ADM of the gallbladder concomitant with GB carcinoma. Two of these 3 patients had segmental-type ADM, and in these cases, axial oblique images obtained by computed tomography (CT) showed circumferential wall thickening in the mid-portion of the gallbladder with luminal narrowing and abnormally intense mucosal enhancement, representing the typical ‘hourglass’ morphology of segmental ADM (Fig. 1A, B).

In the remaining patient with fundal-type ADM, CT imaging revealed a nodular thickening of the gallbladder fundus (Fig. 1C). The imaging also visualized the small RAS as well as the fundal localization and regular thickening, all characteristic of fundal-type ADM. Notably, the preoperative examination of all 3 cases did not suggest a GB malignancy, although the initial exclusion of GB cancer can be problematic in segmental and fundal ADM cases. Macroscopically, the patients

<table>
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<th>Characteristic</th>
<th>ADM of the GB (n = 93)</th>
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<tbody>
<tr>
<td>Male/female</td>
<td>48/45</td>
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<tr>
<td>Age (mean ± SD)</td>
<td>58.0 ± 11.8</td>
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<table>
<thead>
<tr>
<th>Type of ADM</th>
<th>Diffuse</th>
<th>Segmental</th>
<th>Fundal</th>
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<tbody>
<tr>
<td></td>
<td>23</td>
<td>44</td>
<td>26</td>
</tr>
</tbody>
</table>

| Presence of GB stones | 74 (79.6%) |

<table>
<thead>
<tr>
<th>Surgical approach</th>
<th>Laparoscopic</th>
<th>Open</th>
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<tbody>
<tr>
<td></td>
<td>86</td>
<td>7</td>
</tr>
</tbody>
</table>

| Concomitant with GB carcinoma | 3 |

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age (yrs)</th>
<th>Type of AMD</th>
<th>Pathology</th>
<th>Stage*</th>
<th>Gallstone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>55</td>
<td>Segmental</td>
<td>tub1</td>
<td>II</td>
<td>Present</td>
</tr>
<tr>
<td>Female</td>
<td>50</td>
<td>Segmental</td>
<td>pap</td>
<td>I</td>
<td>Present</td>
</tr>
<tr>
<td>Male</td>
<td>75</td>
<td>Fundal</td>
<td>pap</td>
<td>I</td>
<td>Present</td>
</tr>
</tbody>
</table>

*tub1, well-differentiated adenocarcinoma; pap, papillary adenocarcinoma.

*Stage was evaluated according to the TNM system of the International Union Against Cancer (UICC).
with segmental ADM showed almost normal mucosa in the neck compartment proximal to the annular stricture, but there was deteriorated mucosa in the fundal compartment distal to the annular stricture with chronic inflammation (Fig. 2A, B). Hematoxylin & eosin staining of this severely inflamed and deteriorated mucosa revealed partial invasion of the early-stage adenocarcinoma into the muscularis propria of the gallbladder (Fig. 3A). In addition, the adenocarcinoma was evident in the fundal epithelium distal to the annular stricture.

![Fig. 1](image1.png)

**Fig. 1**  A, a 55-year-old man with segmental ADM concomitant with primary GB carcinoma. CT scans of segmental ADM revealed a thickened gallbladder wall with the typical rosary sign, which is formed by the enhanced proliferative mucosal epithelium, with the intramural diverticula surrounded by the unenhanced hypertrophied muscle coat of the gallbladder (arrow); B, a 50-year-old woman with segmental ADM concomitant with primary GB cancer. Axial oblique images by CT show circumferential wall thickening in the mid-portion of the gallbladder with luminal narrowing and abnormally intense mucosal enhancement, revealing the typical hourglass morphological feature of segmental ADM (arrow); C, a 75-year-old man with fundal ADM concomitant with primary GB cancer. Axial CT scan shows oval-shaped focal thickening at the fundal portion of the gallbladder (arrow).

![Fig. 2](image2.png)

**Fig. 2**  A, Sporadic Rokitansky-Aschoff sinuses (RAS) and severe chronic cholecystitis were observed in the fundal compartment; B, There was almost normal mucosa in the neck compartment proximal to the annular stricture; however, the fundal compartment showed deteriorated mucosa distal to the annular stricture, with chronic inflammation; C, Sporadic RAS were situated at the fundus of the gallbladder with normal background mucosa and no inflammation.
on a background of severe inflammation (Fig. 3B).

In the GB cancer arising from the fundal ADM (Fig. 2C), adenocarcinoma of the smooth muscle cells was detected within an aggregation of cystically dilated glandular structures surrounded by a hyperplastic smooth muscle tissue, with nuclear atypia apparent in the glandular epithelium (Fig. 3C).

**Discussion**

ADM of the gallbladder is a common, distinct, non-inflammatory, and benign condition. Kotoh et al. were the first to report noninvasive carcinoma of the gallbladder arising in localized-type ADM, in 1988 [7]. Interestingly, although several subsequent studies demonstrated a relationship between GB carcinoma and ADM of the gallbladder, such an association remains controversial [1,8-12]. One point that is well established is that GB cancer develops subsequently to segmental-type ADM, typically in the epithelium of the fundal compartment distal to the annular stricture. It is thus conceivable that such an annular stricture obstruction could generate sufficient intraluminal pressure and cholestasis in the fundal compartment to induce malignant epithelial changes in the mucosa that would be likely to differentiate into GB cancer.

Actually, in light of our present series, we considered that GB carcinoma developed in the mucosa of the fundal compartment distal to the annular stricture in a patient with segmental-type ADM, and based on this we propose that ADM of the segmental type might be a risk factor for subsequent GB carcinoma due to the chronic inflammatory process ongoing in the gallbladder fundus.

In the present analysis, GB cancer developed in one patient (1.1%) with fundal-type ADM. It should be noted that the fundal type of ADM of the gallbladder might be associated with gallstone formation, and it is well understood that infections induced by certain viruses, bacteria, parasites, or foreign bodies and the following prolonged inflammation are identified as grave risk factors for the development of specific cancers [13]. Gallbladder stone-associated cholecystitis is carcinogenic to humans, according to the International Agency for Research on Cancer and based on various experimental and clinical reports [14,15]. Recent studies also demonstrated that inflammatory cell infiltration is both necessary and sufficient to accelerate carcinogenesis, with an increase in prostaglandin E2 production leading to the acquisition of tumor-forming ability.

![Fig. 3](image)

**Fig. 3** A, H&E staining of deteriorated mucosa with chronic severe inflammation at the part of ADM closest to the annular stricture revealed partial invasion of the adenocarcinoma into the muscularis propria of the gallbladder; B, Segmental ADM concomitant with primary GB cancer. A gallbladder adenocarcinoma was evident in the epithelium of the fundal compartment distal to the annular stricture on a severe inflammation background; C, In the GB cancer arising from the fundal ADM, adenocarcinoma of the smooth muscle cells was detected within an aggregation of cystically dilated glandular structures surrounded by a hyperplastic smooth muscle tissue, with nuclear atypia in the glandular epithelium.
and particularly suppressing the immunological host-defense against tumors [16, 17].

Angiogenesis, cell motility, and the metastatic potential of tumor cells converted from regressive cells are also augmented in parallel with their malignant potential [18]. Several previous investigators reported the CT findings for differentiating gallbladder cancer from chronic cholecystitis or adenomyomatosis. They indicated that a thickened gallbladder wall with disruption or obliteration of the normal layered pattern of the wall suggests cancer [19]. However, no previous studies focused on the differential diagnosis between fundal-type ADM and localized chronic cholecystitis. Our present findings suggest that fundal-type ADM of the gallbladder could also be a contributor to the development of GB cancer, even if the ADM is considered as either the fundal or diffuse type and has very small pockets.

As expected, the differentiation between ADM and GB cancer remains a clinical challenge, because ADM and early-stage, wall-thickening-type GB cancer are often included together in the differential diagnosis due to their similarity in appearance on radiological imaging [4,20,21]. In fact, a previous report noted that approx. 40% of ADM patients were found to be in advanced stages of GB cancer, despite periodic follow-ups [22]. The possible reasons for such an outcome include the lack of symptoms and a negative diagnosis based on both imaging and serum tumor markers such as the carcinoembryonic antigen level and the carbohydrate antigen 19-9 level.

In our series, all three ADM-associated GB cancer cases were diagnosed at Stage II or lower, and the patients achieved a good outcome. Although ADM is not generally considered a premalignant lesion, previous studies and case reports suggest the malignant potential of ADM, and segmental-type ADM is known to have an increased risk of carcinogenesis [1,23]. It is difficult to prove whether a cancer truly arose from RAS or a surface in situ cancer extended into RAS. In addition, as the carcinogenesis of GB cancer correlates with the presence of gallstones and/or inflammation, the accompanying gallstones and/or inflammation tend to be considered responsible for the carcinogenesis rather than the presence of ADM itself. Although the malignant potential of ADM remains unclear, clinicians should keep in mind that a diagnosis of early GB cancer is very difficult in the context of preceding ADM.

It was also reported that especially segmental ADM in elderly patients presented a high risk of the development of GB cancer [23]. Therefore, although it has been thought that all of the gallbladder with RAS would be not an indication for surgical resection, preventive cholecystectomy should be considered in patients with repeated clinical symptoms and segmental ADM, especially in elderly patients.

In conclusion, the results of our study suggest that a preventive cholecystectomy could be useful in ruling out GB cancer, even for asymptomatic ADM cases because preceding ADM may confound the early detection of GB cancer. This study has some limitations associated with errors and biases inherent in a small retrospective study with a limited follow-up period, and thus large cohort studies are recommended to further evaluate the management of this tumor. To this end, we are continuing to collect epidemiological and pathological data.

References

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