

# Gallbladder's adenomyomatosis. Critical aspects for surgical decision

## Adenomiomatosis de la vesícula biliar. Aspectos críticos para la decisión quirúrgica

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### Keywords:

adenomyomatosis, gallbladder, gallbladder cancer, cholecystectomy, biliary tract.

### Palabras clave:

adenomiomatosis, vesícula biliar, cáncer vesícula, colecistectomía, sistema biliar.

### ABSTRACT

Adenomyomatosis of the gallbladder is a benign, pseudotumoral pathology, frequently diagnosed incidentally and rarely considered in clinical practice. The interest of this communication is to establish an accurate diagnosis of gallbladder adenomyomatosis, considering common risk factors with gallbladder cancer to evaluate the safe indication of cholecystectomy in a condition defined as benign. This paper is a retrospective, observational series of cases of 13 patients with a diagnosis of gallbladder adenomyomatosis that studies clinical and imaging diagnosis, surgical procedure performed, morbidity, and mortality. This study included eight women and five men with a mean age of 65.7 years. Nine cases (69.2%) were symptomatic; 46.1% had signs of biliary dysfunction, and 23.3% suffered pain and nonspecific digestive symptoms. The remaining 15.3% were asymptomatic, and another 15.3% were incidental findings during hepatectomies. Ultrasound was diagnostic in 92.3% of patients. Laparoscopic cholecystectomy was performed in 76.9% of cases, conventional cholecystectomy in 15.3%, and one patient chose conservative management. There was no mortality or significant complications. The indication of cholecystectomy for adenomyomatosis by asymptomatic or incidental clinical presentation in the absence of gallstones is only justified in the case of persistent uncertainty diagnosis.

### RESUMEN

La adenomiomatosis de la vesícula biliar es una patología pseudotumoral, benigna, de diagnóstico frecuentemente incidental y poco considerada en el ámbito clínico. El interés de esta comunicación se vincula con la necesidad de establecer el diagnóstico preciso a los efectos de indicar la colecistectomía, considerando que existen factores de riesgo comunes con el cáncer de vesícula en una patología definida como benigna. Se realizó un análisis retrospectivo, observacional, de 13 pacientes con diagnóstico de adenomiomatosis vesicular; se analizó: diagnóstico clínico e imagenológico, procedimiento realizado y morbimortalidad. Fueron incluidos ocho mujeres y cinco hombres con edad media de 65.7 años. Fueron sintomáticos 69.2% de los casos; 46.1%, tenían signos de disfunción biliar y 23.3% sufrían dolores y síntomas digestivos inespecíficos. El 15.3% eran asintomáticos y otro 15.3% fueron hallazgos incidentales en el curso de hepatectomías. La ecografía fue diagnóstica en 92.3% de los pacientes. Se realizó colecistectomía laparoscópica en 76.9% de los casos, convencional en 15.3% y un paciente optó por manejo conservador. No existieron mortalidad ni complicaciones significativas. La indicación de colecistectomía por adenomiomatosis en las formas asintomáticas o incidentales y en ausencia de litiasis vesicular sólo se justifica frente a la incertidumbre diagnóstica persistente.

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Received: 01/07/2024  
Accepted: 03/27/2024



### Abbreviations:

18FDG = 18-fluorodeoxyglucoside.  
ADM/GB = adenomyomatosis of the gallbladder.  
MRI = magnetic resonance imaging.  
RA sinuses = Rokitansky-Aschoff sinuses.  
CT = computerized tomography scan.

### INTRODUCTION

In routine clinical practice, the most frequent gallbladder pathologies are lithiasis and cancer; however, there are other diseases of lower incidence, but with clinical

**How to cite:** Ruso-Martínez L, Espinosa-Nan G. Gallbladder's adenomyomatosis. Critical aspects for surgical decision. Cir Gen. 2024; 46 (1): 54-59. <https://dx.doi.org/10.35366/117369>

and healthcare aspects of great interest. Adenomyomatosis of the gallbladder (ADM/GB) is a degenerative and proliferative pathology of controversial pathogenesis linked to inflammatory and mechanical factors derived from its frequent association with gallstones. Its origin is postulated in epithelial growth stimulated by chronic inflammation secondary to lithiasis or excessive bile absorption at the gallbladder wall level. It is considered a benign disease and is little known by clinicians. Its diagnosis is usually incidental during liver ultrasound.

When faced with the diagnosis of ADM/GB, the main aspects to consider are a) to achieve diagnostic certainty based on a pseudotumorous imaging pattern in a nonspecific or asymptomatic clinical context; b) to evaluate the existence of risk factors common to GB cancer; c) the patient's fear of a gallbladder "tumor" and d) the surgeon's certainty to safely assume the decision to perform cholecystectomy.

The aim of this report is related to the need to make an accurate diagnosis of ADM/GB, considering that it has common risk factors with GB cancer to establish the indication for cholecystectomy for a benign and sometimes asymptomatic disease.

## MATERIAL AND METHODS

This is a retrospective, observational review of a series of 13 patients with a diagnosis of ADM/GB, analyzing age, sex, clinical and imaging diagnosis, procedure performed, and morbimortality. An analysis was made of the literature on the subject, the current definition and pathogenesis of ADM, its possible risk of GB cancer, as well as the need to establish a safe preoperative diagnosis, which allows informing the patient and making a surgical decision with the right elements of technical judgment and safety.

The present work has the approval of the CASMU-IAMPP Ethics Committee, the signed consent of the patients included in the study, and is registered in the MSP (No. 7649061). The authors declare that they have received no funding and have no conflict of interest.

## RESULTS

In the period between March 2012 and July 2020, 6,872 cholecystectomies were performed in the Department of Surgery of CASMU-IAMPP; among them, an imaging diagnosis of ADM/GB was made in 13 cases (0.18%); eight women and five men. The ages ranged from 41 to 87 years (mean 65.7). Nine cases (69.2%) were symptomatic; six of them (46.1%) had signs suggestive of biliary dysfunction and three cases (23.3%) had nonspecific digestive pain and symptoms; two cases (15.3%) were asymptomatic, and two others (15.3%) were incidental findings in the course of hepatectomies for cancer: one metastasis of colorectal carcinoma and one hepatocellular carcinoma.

With ultrasonography the diagnosis was made in 12 cases (92.3%); in the remaining case, a confirmatory magnetic resonance cholangiography was performed due to diagnostic doubt. One patient with nonspecific symptoms opted for follow-up.

Ten (76.9%) laparoscopic cholecystectomies were performed, and in the two cases associated with cancer, the procedure was conventional surgery. The anatomopathological studies showed focal ADM in two patients, and in the other 10, it was located in the vesicular fundus. No malignant cells were found in any case. Gallbladder lithiasis was observed in five cases (38.4%), which represents 0.07% of the total number of cholecystectomies in the period.

There was no mortality or complications except for a urinary tract infection. In the operated cases, hospital discharge was granted in the first two postoperative days in 10 cases, and no evolutionary controls were indicated once the pathologic diagnosis of ADM was confirmed. Patients with hepatectomies were discharged on the fourth and sixth postoperative days. The case that did not undergo surgery was submitted to clinical and ultrasound control and is asymptomatic and without imaging changes after 53 months of follow-up.

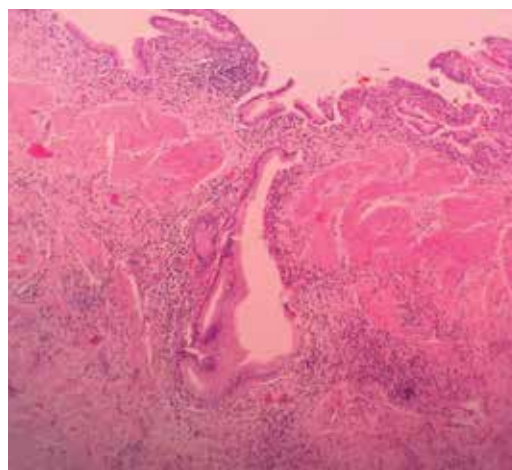
## DISCUSSION

Prior to 1960, multiple terms were accepted to nominate ADM/GB (hyperplastic adenomatosis,

adenomyoma, cystic cholecystitis, proliferative glandular cholecystitis, intramural diverticulosis, hamartoma) until the publication of Jutras,<sup>1</sup> who defined it as a degenerative and proliferative disease of the GB. Adenomyomatosis is now the sole term, although “adenomyosis” is still frequently used. It is considered to be a benign disease, although, in 1988, Katoh<sup>2</sup> reported a noninvasive, localized carcinoma in the breast of a ADM/GB female patient, which prompted interest relating to cancer.

ADM/GB predominates in adults over 50 years of age. This study shows a higher mean age (65.7 years) and the finding of between 1 and 9% of the population aged 65.7 years<sup>3</sup> of the cholecystectomy specimens in this series was much lower (0.07%). In this report, the incidence of associated vesicular lithiasis (38.4%) is in accordance with the literature, which shows an incidence between 36 and 95%.<sup>4</sup> Inflammatory and mechanical mechanisms are postulated in the pathogenesis of ADM/GB. The association between gallbladder stones and the chronic inflammatory changes they produce suggests that epithelial growth is stimulated by permanent inflammation.<sup>5</sup> However, it is also postulated that excessive bile absorption at the level of the vesicular wall generates inflammation that stimulates epithelial growth. Other origins of parietal inflammation have been cited, such as chronic pancreatic/vesicular reflux, especially in patients with abnormal implantation of the Wirsung duct at the level of the common bile duct.<sup>6,7</sup> In addition, alterations in vesicular motility due to neuromuscular hyperactivity increase intraluminal pressure, push the epithelium towards the muscular layer, and produce its transformation to diverticulum, forming the Rokitansky-Aschoff sinuses (RA sinuses) (Figure 1).<sup>8</sup>

The diagnosis of ADM in our series was preoperative in 92% of the cases; in all cases, an ultrasound scan was the first study. The diagnostic efficacy of ultrasound is related to the high incidence of gallbladder stones and the high level of training in the identification of biliary anatomy in our environment. ADM does not have exclusive symptoms; they overlap with those of cholelithiasis, and it is difficult to differentiate between the two. The incidental finding of ADM is discovered in the



**Figure 1:** Gallbladder (H&E 2x). The microscopic appearance of a Rokitansky-Aschoff diverticulum within marked muscular hypertrophy, characteristic of vesicular adenomyomatosis, is shown.

pathological examination of cholecystectomy specimens for symptomatic gallbladder lithiasis and is observed in 7% of the autopsy series.<sup>9</sup> Cholecystectomy may be a therapeutic test when it presents without associated lithiasis and nonspecific symptomatology. Exceptionally, it may present as an acute picture of acalculous cholecystitis.<sup>10</sup> Consequently, imaging is critical for definitive and differential diagnosis.

Associated with the diagnosis of ADM, it is important to rule out GB cancer, and the immediate question emerges: How reliable is imaging to accomplish this with certainty?<sup>11</sup> The efficacy of abdominal ultrasound and computed tomography (CT) scan are similar; both can accurately diagnose ADM. Ultrasonography has a sensitivity of about 65%. Vesicular wall thickening (defined as greater than 3 mm) is a suggestive sign of ADM, always present but not very specific and seen in 25% of cases.<sup>12,13</sup> Other related entities, including cancer, xanthogranulomatous cholecystitis, polyps, lipomas, adenomas, and even acute cholecystitis, should be considered. Consequently, imaging evaluation should rule out the diagnosis of GB cancer, whether the wall thickening is localized or diffuse.<sup>5</sup>

Other signs suggestive of ADM are pseudocystic mural images corresponding to AR sinuses and acoustic artifacts due to intramural

calcific lithiasis with a “comet tail” appearance,<sup>5</sup> which is a particular sign of ADM. Anechoic luminal content can usually be visualized due to biliary mud or lithiasis.<sup>14</sup> There are different types of images associated with parietal thickening that characterize ADM: a) diffuse type, encompassing the entire organ and wall, containing multiple cysts corresponding to the RA sinuses and “kite tail” artifacts; and b) segmental type with annular wall thickening, focused to the medial part that gives the GB an hourglass appearance. In short, the most reliable diagnosis of ADM in a thickened wall is when associated with large AR sinuses, i.e., larger than 3 mm.<sup>11</sup>

Endoscopic ultrasound improves sensitivity for differential diagnosis of GB cancer, but it is an invasive test that must be accurately indicated.<sup>15</sup> It has recently been reported that high-resolution ultrasound would be particularly effective for the diagnosis of GB cancer, with a sensitivity equivalent to magnetic resonance imaging (MRI).<sup>16</sup> The use of contrast-enhanced ultrasound (intravenous injection of hyperechoic microbubbles) has also been reported to enhance the differential and definitive diagnosis of ADM. This technique is inexpensive, avoids radiation and nephrotoxic contrast agents, but is highly operator dependent.<sup>17</sup>

CT scan has a sensitivity of 50-75% for the diagnosis of ADM,<sup>18</sup> but it is not a very effective study for differentiating ADM from GB cancer.<sup>19</sup> Still, some tomographic images are particular, for example, the “pearl necklace rosary” sign, which is produced by the combination of a non-contrast proliferating muscular layer surrounding proliferative mucosal epithelium enhanced by intramural diverticula and the “cotton ball” sign, which consists of gray dots enhanced in a thickened wall on contrast-enhanced CT and is more evident when the RA sinuses are small.<sup>11,16,20</sup>

MRI can provide greater precision in case of diagnostic doubt (*Figure 2*). In fact, it has a higher sensitivity (73 vs. 80.3%) and specificity (96.3 vs. 98.2%) than ultrasound.<sup>16</sup> Here, GB wall thickening can be evidenced on T1 and T2 scans. RA sinuses typically appear hyperintense on T2 and hypointense on T1, showing no contrast enhancement. The conjunction of

parietal thickening and intramural diverticula with the “string of pearls sign” distinguishes ADM from other etiologies and is seen on T2 as multiple high-intensity cavities in the vesicular wall. This pearl sign is more notorious on cholangio-MRI.<sup>21,22</sup>

On positron emission tomography (PET scan), the ADM usually does not uptake 18-fluorodeoxyglucose (18FDG) and has lower uptake compared to the liver ( $SUV < 2.5$ ). It is useful for differential diagnosis because GB cancer is usually hypermetabolic. However, the acute inflammatory reaction surrounding AR sinuses can generate an increased 18FDG uptake and result in a false-positive result. The PET scan is not indicated for the diagnosis of ADM but can help to rule out cancer when the uptake of the marker is low.<sup>23</sup>

In short, due to the diagnostic efficacy that arises from the conjunction of different types of images, anatomopathological studies are usually omitted in the presence of previously analyzed signs, and biopsy is not postulated as necessary.<sup>5</sup>

A second issue is the malignant potential of genuine ADM/GB. While it is difficult to assert that ADM is a cancer risk factor, the inflammatory condition underlying its origin has been considered a potential carcinogen.<sup>24,25</sup>



**Figure 2:** Cholangio-MRI. View of a fundus segmental adenomyomatosis. Parietal thickening with hypercapillary foci in the fundus is seen. In T2, the Rokitsky-Aschoff sinuses can be visualized (arrow) to differentiate adenomyomatous hyperplasia from vesicular carcinoma.



Some authors have reported a relationship between GB cancer and ADM/GB in up to 25% of cases.<sup>26</sup> Although, in general, ADM is not considered to have malignant potential, both entities have in common factors that favor oncogenesis.

When surgery is indicated due to increased pain or other symptoms, an accurate differential diagnosis between ADM and GB cancer is an important element in choosing the appropriate procedure and avoiding influencing the oncologic prognosis.

The absence of cholelithiasis is an independent risk factor linked to GB cancer. The Moon paper<sup>27</sup> shows that the group of patients with ADM had a significantly higher rate of gallstones compared to the group with GB cancer, suggesting that the absence of stones in cases of unclear imaging diagnosis allows inferring the existence of gallbladder cancer.

Morikawa,<sup>3</sup> in 93 cholecystectomies with ADM/VG confirmed by pathology, mentions that 79.6% had associated gallbladder lithiasis, and in 3.2%, an early gallbladder carcinoma was detected, without any preoperative image suggesting it. In the present study, 61.6% of the cases were not associated with gallbladder lithiasis; however, malignancy was not verified in the specimens studied.

A well-established aspect is that GB cancer usually develops in the segmental type of ADM, in the distal fundus sector, and that this location can be considered a precancerous condition (*Figure 3*).<sup>2</sup> Therefore, the difficulty in early diagnosis of GB cancer in the setting of ADM with gallbladder stones is evident, and physicians should be aware of the same when planning the sequence of studies.<sup>2,28</sup>

Therapeutic decision-making in asymptomatic cases without associated vesicular pathology is complex and controversial because, despite its proliferative characteristics -pseudotumorous- ADM is a lesion with low malignant potential. In this case, the tendency is to avoid surgical treatment to minimize the risks of surgery, which allows a "watch and wait" strategy with periodic controls.<sup>5</sup>

When assuming the indication for surgery, one must consider the surgeon's conviction and certainty that he/she has completed a



**Figure 3:** Image of the open and evacuated gallbladder with pseudotumoral aspect. A parietal thickening may be due to extensive muscular hypertrophy and intramural cavities.

process that allows him to guarantee the diagnosis of ADM and the patient's consent and understanding in terms of overcoming his fears in a situation whose most practical solution is cholecystectomy, but over with the risk of a particularly serious complication such as surgical lesion of the biliary tract, which is observed in a low percentage of cases, but whose transcendence and poor prognosis cannot be avoided.

## CONCLUSIONS

The present analysis verifies that ADM/GB is an incidental imaging finding, usually associated with gallbladder lithiasis, with high diagnostic safety efficacy by ultrasound, CT scan, and MRI. It is considered a disease with low malignant potential, even though it shares risk factors with GB cancer. This series shows the absence of neoplasia in all the pieces studied. The indication of cholecystectomy in asymptomatic forms without lithiasis is only justified in the face of persistent diagnostic doubt.

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