Journal of Visceral Surgery (2017) xxx, xxx—xxx

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REVIEW

# Gallbladder adenomyomatosis: Diagnosis and management

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**KEYWORDS**
Adenomyomatosis;
Cholecystectomy;
Gallbladder;
Adenocarcinoma;
Rokitansky-Aschoff sinus

**Summary** Gallbladder (GB) adenomyomatosis (ADM) is a benign, acquired anomaly, characterized by hypertrophy of the mucosal epithelium that invaginates into the interstices of a thickened muscularis forming so-called Rokitansky-Aschoff sinuses. There are three forms of ADM: segmental, fundal and more rarely, diffuse. Etiology and pathogenesis are not well understood but chronic inflammation of the GB is a necessary precursor. Prevalence of ADM in cholecystectomy specimens is estimated between 1% and 9% with a balanced sex ratio; the incidence increases after the age of 50. ADM, although usually asymptomatic, can manifest as abdominal pain or hepatic colic, even in the absence of associated gallstones (50% to 90% of cases). ADM can also be revealed by an attack of acalculous cholecystitis. Pre-operative diagnosis is based mainly on ultrasound (US), which identifies intra-parietal pseudo-cystic images and ''comet tail'' artifacts. MRI with MRI cholangiography sequences is the reference examination with characteristic ''pearl necklace'' images. Symptomatic ADM is an indication for cholecystectomy, which results in complete disappearance of symptoms. Asymptomatic ADM is not an indication for surgery, but the radiological diagnosis must be beyond any doubt. If there is any diagnostic doubt about the possibility of GB cancer, a cholecystectomy is justified. The discovery of ADM in a cholecystectomy specimen does not require special surveillance.


## Introduction

Adenomyomatosis (ADM) of the gallbladder (GB) is a frequent pathology, but it is little known to most clinicians. Its terminology has evolved. Multiple terms that were in use before 1960 (hyperplastic adenomyosis, adenomyoma, adenofibromyoma, cystic cholecystitis, proliferative glandular cholecystitis, intramural diverticulosis, hamartoma...) were simplified by Jutras [1] who defined ADM as a degenerative and proliferative GB disease. We now retain the single term adenomyomatosis, synonymous with the less-commonly used adenomyosis. ''Gallbladder adenomyomatosis'', the most widely used term in English literature, is also recommended by Asian authors [2].

The aim of this review is to examine the pathological, epidemiological and diagnostic characteristics of ADM, to

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http://dx.doi.org/10.1016/j.jviscsurg.2017.06.004
1878-7886/

clarify the therapeutic indications, and to define any potential connection between ADM and GB cancer.

## Pathological findings

There are three macroscopic forms of ADM (Fig. 1):

- the segmental form (> 60%), located between the GB neck and fundus, which constitutes a true cholecystic diaphragm that separates the GB into two communicating zones;
- the fundal form (30%) which is limited to the GB fundus with a dimple overlying an area of fundal wall thickening (In rare cases, it may be associated with the segmental form [2,3]);
- the rare diffuse form (<5%), which corresponds to parietal thickening involving the entire GB wall [3].

ADM is a benign, acquired lesion characterized by epithelial, mucosal, and muscular (smooth muscle) hypertrophy (Figs. 2 and 3). The GB wall has an overall thickened appearance (sometimes > 10 mm) and contains diverticula or Rokitansky-Aschoff's sinuses (RAS), first described by Rokitansky in 1842 and then by Aschoff in 1905; these correspond to mucosal invaginations into the muscularis of the GB wall. RAS are necessary for diagnosis but are not pathognomonic; they may also be present especially in case of xanthogranulomatous cholecystitis. However, in the case of ADM, RAS are particularly deep, associated with wall thickening, and may extend beyond the muscular layer.

Confirmation of the diagnosis of GB ADM must be associated with a careful search to rule out adenocarcinoma, within or at a distance from RAS [2,4], since the two pathologies co-exist frequently (cf infra).

## Epidemiology

ADM is typically diagnosed beyond the age of 50—60, with a balanced male to female ratio [2,5—7]. Fewer than 10 cases have been reported in children [8—10] in the first year of life. ADM is most often incidentally discovered on the operative specimen after a cholecystectomy performed for another reason (symptomatic lithiasis, cholecystitis, polyp, etc.) with a prevalence of 1% to 9% [2,3,11]. In 1963, Bricker and Halpert reported the prevalence of ADM to be 7% in a large autopsy series [12].

## Pathophysiology

The pathogenesis of ADM is not formally established and several predisposing factors are possibly intertwined. The pathophysiology of ADM in adults is potentially different from infantile forms for which no data exist.

Motility disorders of the GB (neuromuscular hyperactivity) that cause increased intra-luminal pressure and protrusion of the epithelium into the muscularis have been suspected to play a major role. Indeed, Beilby et al. demonstrated that cystic duct spasm associated with abnormal contraction of the hypertrophied GB muscularis resulted in pain [13]. Jutras had also demonstrated, some years before, the presence of a spastic ''sphincter'' in the proximal cystic duct [1]. Since this historical work, no recent study has confirmed or contradicted these hypotheses.

Chronic GB inflammation, whatever its origin, also appears to play a role. Thus, several authors have reported the association between ADM and anomalies of the biliopancreatic junction, although no formal causal link has been demonstrated [14—16]. Chronic reflux of pancreatic fluid into the GB may explain the occurrence of ADM, at least in part [17,18], since chronic exposure to pancreatic secretions has been shown to result in hyperplasia of the GB epithelium, particularly in patients with a pancreaticobiliary maljunction where the pancreatic duct empties into the choledochus [16]. In the retrospective series of Chang et al., 50% of patients with ADM had such an anomaly [15]. Tanno et al. found that 32% of patients with bilio-pancreatic junction anomalies also had ADM [14], and 86% of these patients had the fundal form. Segmental forms have also been reported in this context [19]. Finally, some authors have suggested excessive reabsorption of bile by the GB wall to be a factor that triggers inflammatory phenomena. Chronic inflammation of the biliary tract may therefore favour the development of ADM, but it is also recognized as a potent biliary carcinogen (cholangiocarcinoma) [20]. It is difficult to say that ADM is a risk factor for biliary cancer, but these two pathologies frequently coincide, and this is perhaps related to the same pro-inflammatory field.

Cholecystolithiasis is present in more than 50% of patients with ADM, and up to 90% with segmental ADM [2,3]. In segmental ADM, gallstones are located predominately in the fundal compartment in 81% of the cases [3]. Oral cholecystography confirmed that the fundal portion of the GB empties poorly [21,22], favouring biliary stasis and a lithogenic environment with cholesterol saturation and decreased bile acids and phospholipids.

## Clinical presentation

ADM is usually asymptomatic (incidentally discovered by imaging or by pathology of the cholecystectomy specimen) or pauci-symptomatic. Rarely, ADM can manifest itself as authentic biliary colic-type pains in the right hypochondrium, but since cholelithiasis is present in half the cases of ADM, it is difficult to impute the specific cause to ADM. These pains, which have also been reported in patients without lithiasis [8,23,24], usually last from a few minutes to a few hours and resolve spontaneously. Often patients report non-specific digestive disorders (fatty food intolerance, flatulence, nausea, vomiting) that become progressively more frequent [5,7]. It is not uncommon for patients to describe pain of many years duration before the connection with ADM is evoked. In these cases of nonspecific symptomatology, ADM remains a diagnosis of exclusion since no specific sign can implicate ADM (cholecystectomy can represent a therapeutic test). ADM can also be revealed by a first attack of acalculous cholecystitis [25].

## Radiological diagnosis and differential diagnostics

Since ADM has no specific symptoms, imaging plays a fundamental role in its differential and definitive diagnosis; ADM accounts for 25% of cases of GB wall thickening (> 3 mm). When confronted with a thickened GB wall, several entities must be considered in the differential diagnosis, related to the GB (cancer, polyp, lipoma, adenoma, acute

Please cite this article in press as: Golse N, et al. Gallbladder adenomyomatosis: Diagnosis and management. Journal of Visceral Surgery (2017), http://dx.doi.org/10.1016/j.jviscsurg.2017.06.004