

## Benign Mimickers of Gall Bladder Carcinoma in Cholecystectomy Specimens: Histopathological Study



### Medical Science

**KEYWORDS :** Benign Mimickers; Gall Bladder Cancer; Histopathology.

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### ABSTRACT

*Carcinoma of the gallbladder (GBC) clinically mimics many benign gallbladder diseases and often escapes detection until advanced stage. Despite the frequency of cholecystectomies, diagnosis of GBC remains problematic in many situations. The aim of this study is to analyze many pathological mimickers of GBC, which may be associated with overdiagnosis and underdiagnosis of this malignancy, as well as to show the prevalence of GBC in a local region of KSA. This analytical retrospective study was performed on 1500 cholecystectomy specimens which were collected through 4 years from 7 governmental Hospitals located in one region in KSA. The surgical materials were received in the central Histopathology laboratory situated in Arar city. Majority of surgical cholecystectomy specimens were done for cholelithiasis. Rokitansky-Aschoff sinuses (RAS) are one of the most important benign mimickers of GBC, they are found in 7.1% of the studied specimens, and adenomyomatosis is another mimicker which was seen in 2%, of gall bladder specimens, whereas GBC diagnosed in 0.8% of cholecystectomy specimens.*

*This study concluded that accurate pathological evaluation of gall bladder disease through patient's history in conjunction with clinical high index of suspicion are prerequisites to detect GBC. Detection of GBC at an early stage is difficult because the symptoms mimic benign gallbladder diseases. Misinterpretation of subtle microscopic abnormalities contributes diagnostic failures in early cases of GBC. Careful attention to any evidence of mural thickening, thorough sampling, particularly in older patients, and close examination of any deeply situated glandular structures are critical.*

### INTRODUCTION

Discarding cholecystectomy specimens without meticulous histopathological examination may be associated with serious outcome in some setting, which is linked to missing many dangerous disorders like porcelain of gall bladder, dysplasia, carcinoma in situ, and early adenocarcinoma, because these lesions go unnoticed without alarming clinical or ultra-sonographic findings (Underwood 2001, Wilkinson 1995, and Siddiqui et al. 2013). In addition to the above facts, RAS may be horizontally oriented and lined by hyperplastic or metaplastic biliary epithelium which can closely simulate GBC (Albores-Saavedra 2000). Gall bladder carcinoma (GBC) is rare and has a comparatively low frequency (Esltik 2010). The Geographic distribution of GBC is varied with highest incidence reported from some south American and south Asian countries (Velo, and Rodrigues et al. 2011). Early diagnosis of GBC is difficult because of its consistent non specific clinical presentation (Khoo, and Nural 2008). Recent studies have implicated various risk factors in the causation of GBC (Jain et al. 2013). Identification of the risk factors helps in selection of patients for prophylactic cholecystectomy and thereby aid in overall prevention of GBC. Latest studies have clearly mentioned and confirmed the role of histopathology in the diagnosis of GBC in routine cholecystectomy specimens making it mandatory and thereby establishing it as an important diagnostic tool for the clinically unsuspected GBC and in the early detection of malignancy which is associated with relatively better prognosis (Kapoor 2006).

### PATIENTS AND METHODS

This retrospective study was carried out on tissue sections of 1500 cholecystectomy specimens, which were introduced from the surgical department. All the patients were seen in the outpatient clinics and were suffering from complaints suggestive of gall bladder diseases. After clinical diagnosis, all patients were subjected to radiographical investigations including ultrasonography, and C T scanning, and then the patients were prepared for surgical interventions. The surgically resected cholecystectomy specimens were fixed in 10% neutral-buffered formalin solution, and sent to the Department of Pathology, Arar Central Hospital, Arar City, Saudi Arabia. The materials were collected through the period from 2011 to April 2015. The Pathology Department received surgical specimens which came from 7 Cen-

tral Hospitals in the Northern Region; KSA including more than 1000 beds. All the clinical data of the patients including age, gender, and clinical complaints were obtained from patient's medical records. All the received surgical specimens were processed then, paraffin-embedded blocks were prepared, and were cut into 3 micron-thick tissue sections. These sections were stained by routine Hematoxylin and Eosin stains, then examined microscopically by two expert pathologists.

### RESULTS

The clinical findings of all patients included in this study which included age groups, gender, morphological types of gall stones, and the clinico-radiological diagnosis were summarized in tables 1, 2, and 3.

**Table 1: Age groups and gender distribution in all cases of cholecystectomy specimens examined.**

Age groups and number of cases		Gender distribution		Total
Males		Females		
20-30	50	20	30	50
31-40	200	50	150	200
41-50	400	100	300	400
51-60	700	150	450	500
61-70	100	25	75	100
71-80	50	10	40	50
Total	1500	505	995	1500

Regarding table 1, majority of cholecystectomy specimens were received from females in age ranged from 51 to 60 years. In the same context most of the patients were suffering from right hypochondrial pain, whereas 3 patients were complaining from mass.

**Table 2: Presenting complains of all included patients**

Complains	Number of cases and %
Pain in right hypochondrium	900
Intolerance of fatty diet	297

Nausea and or / vomiting	200
Abdominal distention and or / constipation	100
Mass in right hypochondrium	3
Total	1500

**Table 3: Morphological types of stones in all cases of cholecystectomy specimens examined:**

Number and types of stones in females			Number and types of stones in males		
Cholesterol	Pigment	Combined	Cholesterol	Pigment	Combined
10	5	-----	10	6	5
70	40	11	60	16	10
10	10	11	10	10	30
20	30	14	20	30	20
100	30	10	40	20	50
50	20	6	10	9	25
260	235	52	140	91	140

In regard to table 3 most cases of cholelithiasis were seen in females, and encompassed 36.5% of cholecystectomy material, and majority of them were cholesterol stones, whereas in males cholelithiasis was found in 24.7% of cases, among them cholesterol stones were detected in 9.3% of patients.

**Table 4: Clinico-radiological diagnosis of all included cases:**

Diagnostic Parameters	Number of cases
Cholelithiasis	918
Acute calculous cholecystitis	384
Acute a calculous cholecystitis	191
Polyp	5
? Malignancy	2
Total	1500

with regard to (Table 4) most of the cholecystectomy specimens were done due to cholelithiasis (61.2%), sonographically, polypoid lesions of the gall bladder were seen in 0.3%, whereas malignancy of gall bladder was suspected in 2 cases (0.1%) out of the 1500 cases of the received specimens.

**Table 5: Gross and microscopic diagnosis of examined cholecystectomy specimens included in the study**

Gross features and number Of cases	Microscopic diagnosis and number of cases
Gall stones	918
Smooth outer surface	200
Rough outer surface	90
Thickened wall > 1cm	> 100
Thickened wall < 1cm	< 180
Ulcerated mucosa	100
Greenish mud	50
Dark black walls	47
Congested walls	50
Dilated cystic duct	25
Mural Polyps	15
> one feature	200
Total	1500

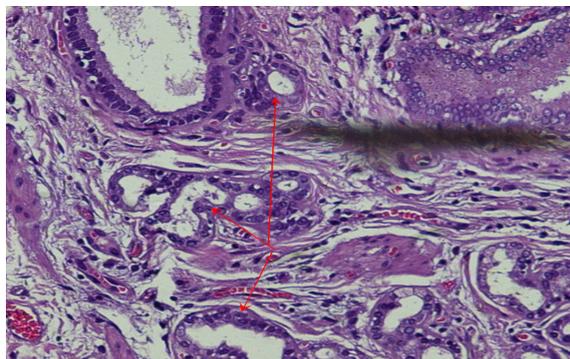
With regards to (Table 5) most of the cholecystectomy specimens that are diagnosed microscopically were chronic calculous cholecystitis, which is seen in 38.7%. Specific forms of chronic calculous cholecystitis were found in many cases and including

many variants which are listed in table 5.

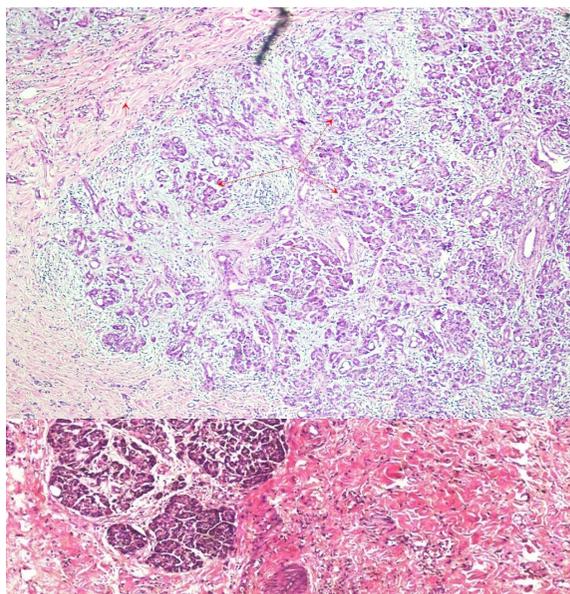
**Table 6: Benign mimickers to GBC in all cases of cholecystectomy specimens studied:**

Benign mimickers	No. of cases
Rokitansky-Aschoff sinuses (RAS)	107
Adenomyomatosis	30
Papillary hyperplasia	30
Cholesterol polyps	10
Porcelain gall bladder	5
Gangrenous cholecystitis with geographical necrosis	133
Adenocarcinoma	12
Total	327

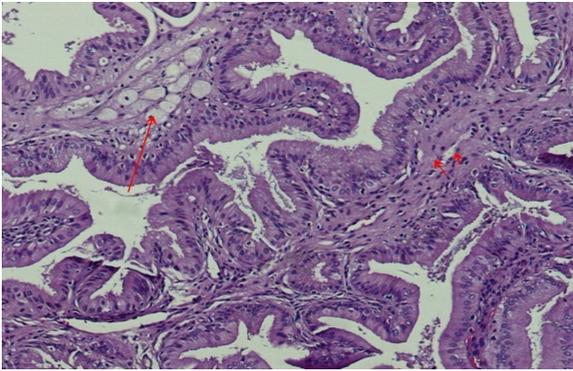
Regarding the benign mimickers of GBC, the transmurally RAS was observed in 7.1% of cases (figure 1), each of adenomyomatosis (figure 2&3) and papillary hyperplasia (figure 4) was diagnosed in 2% of cases. Cholesterol polyps were seen in 0.7% of cases (figure 5), whereas gangrenous cholecystitis with geographical necrosis was found in 8.8% of cases (Table 6). Adenocarcinoma of gall bladder was detected in 0.8% of the cholecystectomy specimens (figure 6).



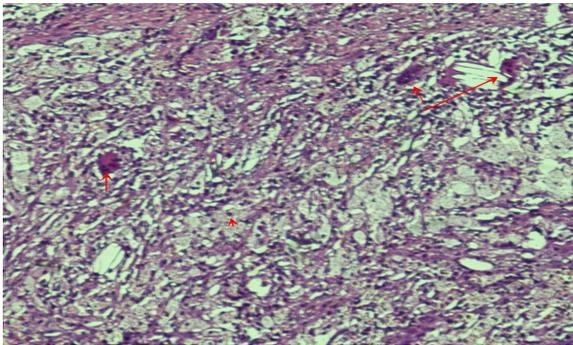
**Fig 1: section in gall bladder showing deeply seated glands in RAS ( arrows) (H&E x200).**



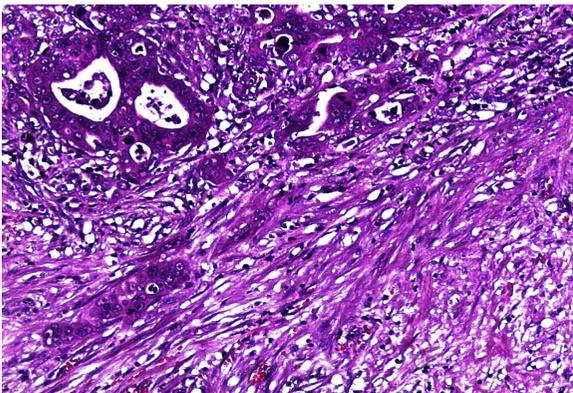
**Fig 3: section in gall bladder showing adenomyoma with marked glandular proliferations encircled by bundles of muscular hypertrophy (H&E x100).**



**Fig 4:** section in gall bladder showing papillary hyperplastic changes with fibrous core (double arrows), and collections of foam cells (long arrow) (H&E x100).



**Fig 5:** section in gall bladder showing cholesterol polyp with foreign body giant cells, cholesterol clefts (long arrows) and collections of foam histiocytes (short arrow) (H&E x100).



**Fig 6:** section in gall bladder showing infiltrating moderately differentiated adenocarcinoma with intramural neoplastic stratified glands (H&E x200).

## DISCUSSION

Histologically, normal gallbladder wall is composed of four layers: mucosa, lamina propria, an irregular muscle layer, and connective tissue. The surface epithelium is composed of a single layer of columnar epithelium. There is no muscularis mucosa or submucosa. Along the hepatic surface, the connective tissue is continuous with the interlobular connective tissue of the liver (Levy et al. 2001). Of the important pathology affecting gall bladder is GBC, which is an uncommon but highly fatal malignancy; fewer than 5000 new cases are diagnosed each year in the United States. The majority are found incidentally in patients undergoing exploration for cholelithiasis (Carriaga and Henson 1995, Hamrick et al. 1982, and Yamaguchi et al. 1996). The most common benign neoplastic mimickers of GBC including

Rokitansky-Aschoffsinuses (RAS), adenoma, adenomyomas, adenomyomatosis, and other polyps. Many studies suggest a correlation between the presence of gallbladder polyps and the risk of GBC (Wistuba et al. 1996, and Okamoto et al. 1999).

In this study most of cholecystectomies were performed for cholelithiasis, which were diagnosed microscopically as chronic calculous cholecystitis (38.7%). Benign mimickers for GBC were observed in the form of RAS which is seen in 7.1% of cases, each of adenomyomatosis and papillary hyperplasia found in 2% of cases, and geographical necrosis that are observed in 9.8% of cases. Adenocarcinoma was seen in 12 cases of the received cholecystectomy specimens. Gall bladder cancer is more common in patients with cholelithiasis, the main mechanism involves the occurrence of cholecystitis, and seems to be the driving force in most regions of the world where GBC is strongly associated with gallstone disease, female gender bias, and age over 65 (Lazcano-Ponce et al. 2001, and Rustagi and Dassanu 2012). Gallbladder polyps larger than 1.5 cm (especially solitary sessile hypoechoic polyps) are associated with a 50% risk of malignancy. Porcelain gallbladder is a risk factor, particularly when there is calcification of the gallbladder mucosa. Chronic gallbladder infection has been implicated as a risk factor for malignant transformation (Kianmanesh et al. 2007). Rokitansky-Aschoff sinuses (RAS) is one of the most important benign mimickers of GBC especially well differentiated tumors, which is widely located throughout gall bladder wall and evenly distributed up to the perimuscular adipose tissue. The extensive and subsequent additional tissue sections may be helpful in the differential diagnosis by detection of the cytologic atypia, mitosis, and intraglandular necrosis which favors malignancy over benign lesions (Albores-Saavedra et al. 2004, Saul 2009, and Terada 2008).

Pathologists should be aware of the presence of glandular structures embedded in the gallbladder wall. This condition does not simply suggest RAS or adenomyomatosis. Both can be confused with adenocarcinoma of gallbladder. However, the glands in the former are usually bland cytologically; and they may show communication with the main gallbladder lumen (Kim et al. 2008, and Pritchard and Yeh 2009).

Extensive necrosis may be seen in cases of gangrenous acute cholecystitis that can be confused with an aggressive neoplastic process. In the same context, extensive tumor necrosis with minimal residual viable tumor may mimic acute gangrenous cholecystitis. The careful and thorough histologic sampling in particular areas without necrosis is critical in these cases with extensive necrosis to reveal any diagnostic viable tumor (Gattuso et al. 2010, Giang et al. 2012, and Saul 2009).

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