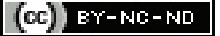Original Article

Catching Gall Bladder Cancer Early- Importance of Cholelithiasis and Radiologist

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ABSTRACT

Introduction: Increased relative risk of Gall Bladder (GB) cancer in patients with gall stones has been reported in literature but there are few reports on nature of stones. However, it is difficult to predict which patient suffering from cholelithiasis and cholecystitis may develop or already has early stages of carcinoma.

Aim: The present study was undertaken to assess the malignant potential and relevance of gall stones, age and gender in GB carcinoma to propose a screening protocol and early intervention for high risk patients.

Materials and Methods: This was a retrospective study done at Moti Lal Nehru Medical College, Prayagraj, Uttar Pradesh, India from May 2012 to May 2019. This study included 200 histopathologically- Fine Needle Aspiration Cytology (FNAC) or postoperative specimen biopsy proven GB carcinoma and 200 control patients with upper abdominal pain but without any evidence of neoplastic changes on USG. All cases and controls were subjected to USG evaluation first followed by plain CT scan with oral contrast only and Contrast Enhanced CT (CECT) scan of whole abdomen as per protocol. Scans were evaluated for detection of gall stone profile in terms of number (solitary/multiple), size (small/large) and density (radio-opaque/radiolucent). The statistical analysis was done by using IBM Statistical Package for the Social Sciences (SPSS) version 18.0.

Results: Male to female ratio in this study was 1:2. GB calculi cannot be considered as bystander as overall 25% patients of both sexes had cholelithiasis. In the present study, 25% who were having carcinoma GB have been detected to have gall stones and out of which 74% were having small calculi. The study showed the association between GB cancer and solitary and multiple large calculi over different age groups to be not statistically significant (p-value=0.3976; χ^2=0.716). Association of small and multiple calculi came out to be highly significantly associated with carcinoma in 67% of patients. Furthermore, it was observed that the association between multiple small calculi and GB cancer over the different age groups came out to be extremely statistically significant (p-value=0.0001; χ^2=28.62). The association between gall stones in GB cancer patients differ statistically significant over the age groups from cases with gall stones in control group (p-value=0.005497; χ^2=7.7082).

Conclusion: From the findings of the study author proposed screening via ultrasound and guided FNAC for females over 40 years of age with multiple small calculi not undergoing immediate cholecystectomy to detect early emergence of carcinoma. It is also suggested that clinicians should post patients with multiple, small GB calculi for cholecystectomy on a priority basis and histopathology should be done in each case of GB wall thickening.

Keywords: Gall stones, Gall bladder carcinoma, Radio-opaque, Radiolucent

INTRODUCTION

Gall bllader carcinoma being the most common malignancy of the biliary tract, ranks 6th among gastrointestinal cancers worldwide [1,2]. Epidemiological studies in India report its prevalence to range from 0.1-3.7 per 100,000 population for males to 0.3-8.9 per 100,000 population for females [3]. However, the magnitude of the problem could be huge especially in the endemic zones of North-east India (Western Bihar and Eastern Uttar Pradesh) where it is the third commonest malignancy of the alimentary tract [4,5].

The median age at presentation is considered to be 67 years [2]. Menopausal females and smokers are considered at higher risk of GB cancer as per various epidemiological studies [6,7]. Cholelithiasis is a well-established risk factor for the development of GB carcinoma [8], and gallstones are present in 74%-92% of affected patients [9].

The GB carcinoma is generally diagnosed incidentally when patients present symptoms of abdominal pain, nausea, vomiting and/ or fever related to co-existent cholelithiasis or cholecystitis. One percent of patients undergoing cholecystectomy for cholelithiasis have an incidental GB carcinoma [10,11]. The majority of patients with GB carcinoma present with advanced disease. Symptoms are typically indolent. Chronic abdominal pain, anorexia, or weight loss is common initial complaints [2]. Physical examination may demonstrate a lump, hepatomegaly and jaundice [12].

Increased relative risk of GB cancer in patients with gall stones has been reported but there are few reports on nature, density and number of stones affecting prognosis [7,13]. Keeping this in mind, there is a need to further study the risk of GB cancer with respect to number, size and type of gall stones. It is difficult to predict which pateint is suffering from cholelithiasis and cholecystitis may develop or already has early stages of carcinoma. A wide array of medical, conservative and surgical approaches is present regarding management of cholelithiasis and cholecystitis. But in absence of a uniform fixed protocol regarding early prediction and preventive surgical management of such patients more prone to develop carcinoma, majority of GB carcinomas are detected late. Hence, this study was conducted to assess the malignant potential of different types and numbers of gall stones via ultrasonography, plain CT with oral contrast and CECT. The present study was undertaken to know the relevance of calculus, age and gender in prediction of GB carcinoma to propose a screening protocol and early intervention for high risk patients.

MATERIALS AND METHODS

This was a retrospective study done at Moti Lal Nehru Medical College, Prayagraj, Uttar Pradesh India from May 2012 to May 2019. Approval for this study was obtained by Ethical Committee of MLN Medical College, Prayagraj, Uttar Pradesh, India.

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Inclusion and Exclusion criteria: 200 patients with histopathologically (FNAC or postoperative specimen biopsy) proven GB carcinoma and 200 control patients with upper abdominal pain but without any evidence of neoplastic changes on USG were included. Subjects below 18 years of age, cases with previous known malignancy or metastasis of other origin apart from GB cancer were excluded.

Study Procedure

All cases and controls were subjected to USG evaluation first followed by plain CT scan (with oral contrast only) and CECT scan of whole abdomen as per protocol. USG examination was performed using LOGIQ- P9 USG machine (GE Healthcare). CECT Scan was done on Revolution ACTs (GE Healthcare). Initially plain axial scans were taken from the domes of diaphragm till the level of iliac crest, after administering 1000 mL of oral iodinated water soluble contrast (20 mL of 350 mgI/mL non ionic water soluble contrast mixed with water to make 1000 mL) with 800 mL half an hour before examination and 200 mL at the time of examination for bowel opacification. Scanning was performed using pitch of 1.0:1, a scanning time of 1.0 sec/rotation, table speed of 10 mm/rotation, 160-180 mAs, and 120 kVp. Later on contrast enhanced scan was done after administering 80-100 mL of non ionic water soluble contrast (350 mgI/mL) depending upon weight of the patient with pressure injector at a rate of 2.0 mL/sec and scans were taken in portal venous phase (50-55 sec after contrast initiation of contrast administration). Images were acquired with slice thickness of 5 mm and reconstruction interval of 0.7 mm followed by Multiplanar Reconstruction (MPR) algorithm both in coronal and sagittal plane.

Scans were evaluated for detection of gall stone profile in terms of number (solitary/multiple), size (small/large) and density (radio-opaque/radiolucent). Size of 10 mm was the cutoff for small and large calculi. Criteria for radio-opaque stones were stones which were hyperdense to bile on CT scan and for radiolucent stones were hyperechoic on USG but isodense to bile on CT scan and hence imperceptible on CT Scan.

STATISTICAL ANALYSIS

The statistical analysis was done using IBM SPSS version 18.0. The statistical test applied here was Chi-square two-tailed test for association with and without Yates correction as required at 5% level of significance or 95% confidence interval.

RESULTS

Female to male ratio in the present study was 2:1. GB calculi cannot be considered as bystander as overall 25% patients of both sexes had cholelithiasis [Table/Fig-1]. However, few patients had carcinoma GB without any evidence of calculus [Table/Fig-2]. Total of 50 patients (25%) who were having carcinoma GB have been detected to have gall stones and out of which 37 patients (74%) were having small calculi [Table/Fig-3,4]. Out of 200 patients, 6.5% had large calculi [Table/Fig-5]. At 5% level of significance, Chi-square without Yates correction two-tailed test showed the association between solitary and multiple large calculi over different age groups to be not statistically significant (p-value=0.3976; χ^2=0.716) [Table/Fig-6].

| Age interval	Gall stone			
	Present	%	Absent	%
30 and below	2	1	5	2.50
31-40	7	3.50	27	13.50
41-50	12	6.00	34	17
51-60	11	5.50	35	17.50
61-70	13	6.50	31	15.50
71 and above	5	2.50	18	9
Total	50	25	150	75

[Table/Fig-1]: Distribution of gall stones according to age in 200 cases of Gall Bladder (GB) cancer patients.
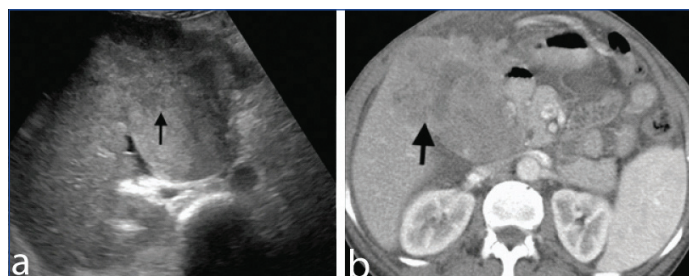

[Table/Fig-2]: Acalculus GB mass. a) A 55-year-old male, trans-abdominal USG reveal large hypoechoic ill-defined mass replacing Gall Bladder (GB) and infiltrating adjacent liver parenchyma. No calculus is seen in mass; b) Axial Contrast Enhanced CT (CECT) scan abdomen reveal large heterogeneously enhancing mass replacing Gall Bladder (GB) and infiltrating adjacent liver parenchyma.
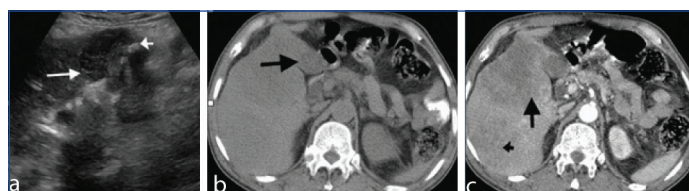
[Table/Fig-3]: GB mass with multiple small radiolucent calculi. a) A 60-year-old male, trans-abdominal USG reveal large hypoechoic ill-defined mass largely replacing Gall Bladder (GB) infiltrating liver parenchyma and presence of multiple small hyperechoic calculi embedded in mass; b) Plain CT scan abdomen reveal large ill-defined hypodense lesion in Gall Bladder (GB) fossa with no radio-opaque calculi; c) Contrast Enhanced CT (CECT) reveals large heterogeneously enhancing mass largely replacing Gall Bladder (GB) infiltrating adjacent liver parenchyma and multiple small ill-defined enhancing metastatic lesions in posterior segment liver.
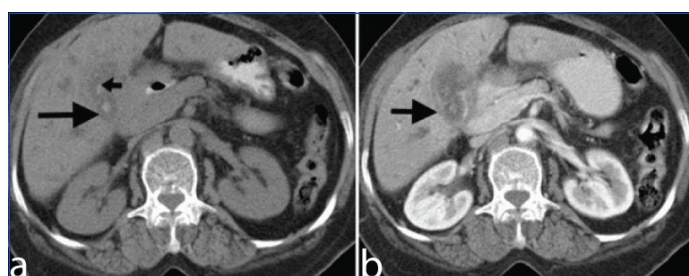
[Table/Fig-4]: GB mass with multiple small radio-opaque calculi. a) A 65-year-old female, plain axial CT scan abdomen reveal ill-defined irregular thickened wall Gall Bladder (GB) and presence of multiple small hyperdense calculi in lumen; b) Contrast Enhanced CT (CECT) scan abdomen reveal irregular thickened enhancing wall Gall Bladder (GB) and small eccentrically enhancing soft tissue infiltrating adjacent liver parenchyma.
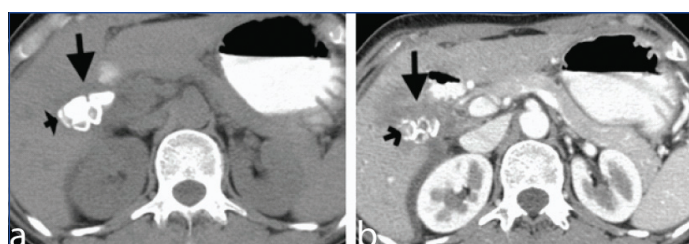
[Table/Fig-5]: GB mass with multiple large radio-opaque calculi. a) A 40-year-old female, axial plain CT Scan abdomen reveal ill-defined isodense soft tissue replacing Gall Bladder (GB) and presence of multiple large hyperdense calculi embedded within the soft tissue; b) Axial Contrast Enhanced CT (CECT) scan abdomen reveal large ill-defined mildly enhancing mass lesion replacing Gall Bladder (GB) lumen infiltrating adjacent liver parenchyma (large arrow) and multiple large hyperdense calculi (small arrow) embedded within the mass.

In [Table/Fig-7], Chi-square without Yates correction two-tailed test showed the association between multiple small calculi and GB cancer over the different age groups to be extremely statistically significant (p-value=0.0001; χ^2=28.62). None of patients had radiolucent solitary small calculus and only 2% of total of 200 patients had radiopaque solitary calculus [Table/Fig-6-8].

In control group of 200 patients with upper abdominal pain or jaundice without GB cancer, 19 had cholelithiasis. [Table/Fig-9] showed that the percent of cases with gall stones in GB cancer patients differ from percent of cases with gall stones in control group and this difference was found to be statistically significant (p=0.005497; χ^2=7.7082).

Age interval	Solitary calculus				Multiple calculi				p-value and Chi-square value
	Radiolucent		Radio-opaque		Radiolucent		Radio-opaque		
	No.	%	No.	%	No.	%	No.	%	
30 and below	0	0	0	0	1	2	0	0	
31-40	0	0	0	0	0	0	0	0	
41-50	0	0	0	0	2	4	2	4	
51-60	1	2	1	2	1	2	1	2	0.3976
61-70	1	2	0	0	1	2	0	0	0.716
71 and above	2	4	0	0	0	0	0	0	
Total	4	8	1	2	5	10	3	6	

[Table/Fig-6]: Relationship of age to large gall stone (≥10 mm) characteristic in 200 Gall Bladder (GB) cancer patients. Chi-square without Yates correction two-tailed test used at 5% level of significance

Age interval	Solitary calculus				Multiple calculi				p-value and Chi square value
	Radiolucent		Radio-opaque		Radiolucent		Radio-opaque		
	No.	%	No.	%	No.	%	No.	%	
30 and below	0	0	0	0	1	2	0	0	
31-40	0	0	1	2	0	0	6	12	
41-50	0	0	0	0	2	4	6	12	
51-60	0	0	2	4	1	2	4	8	0.0001
61-70	0	0	0	0	1	2	10	20	28.62
71 and above	0	0	0	0	0	0	3	6	
Total	0	0	3	6	5	10	29	58	

[Table/Fig-7]: Relationship of age to small gall stone (<10 mm) characteristic in 200 Gall Bladder (GB) cancer patients. Chi-square without Yates correction two-tailed test used at 5% level of significance
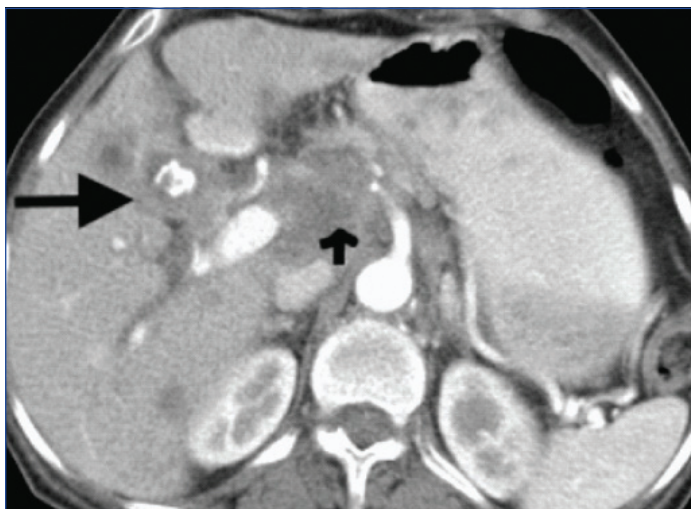
[Table/Fig-8]: Solitary large radio-opaque calculus with GB mass. Contrast enhanced axial CT Scan abdomen reveal irregular thickened enhancing wall Gall Bladder (GB) and enhancing soft tissue at neck infiltrating adjacent liver parenchyma and small enhancing metastatic deposit in posterior segment liver. Multiple enlarged periportal and celiac lymph nodes seen (small arrow).

Cholelithiasis	GB cancer (cases)	GB cancer (controls)	Total	p-value and Chi-square value
Present	50	19	78	
Absent	150	181	322	0.005497
Total	200	200	400	7.7082

[Table/Fig-9]: Presence and absence of calculi in cases and controls.

DISCUSSION

It has been postulated that chronic irritation and inflammation of GB wall with gall stone leads to mucosal dysplasia and is subsequently associated with increased risk of GB carcinoma [14]. Gallstones can be classified as cholesterol, mixed, or pigment stones. In western countries, approximately 75% of GB stones are of cholesterol stones [15]. Detectability of gallstones on CT is affected by their chemical composition. The amount of calcium phosphate or calcium carbonate within gallstones correlates with their visibility on CT. Pigment stones have a higher affinity for calcium carbonate and calcium bilirubinate and generally have higher CT attenuation values. Pure cholesterol stones on the other hand, are lower in attenuation and not as readily detected by CT [15-18].

Regarding ultrasonographic characteristics of gallstones, sonographic criteria for cholesterol stones are stones that float in the GB or stones that produce acoustic shadows without internal echoes from the stones [9]. In a study conducted by Good LI et al., no correlation was found between gallstone type or calcium content and acoustic shadowing. Acoustic shadowing was found to be related to the size of the gallstone. Stones 4 mm or greater in diameter are much more likely to produce distinct sonic shadows compared to smaller stones regardless of composition [19].

In the present study, gall stones were present in 25% of GB carcinoma patients as compared to 74%-92% in earlier studies [2,20]. This statistic in earlier studies may be inflated, as those undergoing cholecystectomy for cholelithiasis are more likely to be diagnosed incidentally or postoperatively with GB cancer. Also, obesity, being a major factor in formation of cholesterol gall stones is still at a lower prevalence in developing countries. Thus, ethnical and geographical based variations must be kept in mind while assessing incidence of GB cancer in patients of cholelithiasis. This may be also be due to other predisposing factors such as chronic Salmonella type infection, exposure to chemicals used in the rubber, automobile, wood finishing, and metal fabricating industries which lead to GB carcinoma apart from gall stones in our studied population [21-23].

Shrikhande SV et al., in their study concluded that in view of lack of absolute proof, cholelithiasis is a co-factor the causation of GB carcinoma [20]. They recommended tailoring of prophylactic cholecystectomy. In the present study, it was found that patients with solitary large calculus were not significantly associated with GB cancer. Hence, not all patients need to undergo prophylactic cholecystectomy.

Most of gall stones in carcinoma patients were found to be in 5th-7th decades of age group with a preponderance of female gender. Female to male ratio in the present study was 2:1 while it was found to be three times more common in females in earlier studies [2,24,25]. Prevalence of fasting on religious grounds in in Northern India might result in increase in presence of small calculi in concentrated bile in both genders which might have led to lesser variation in gender ratio. Presence of small (less than 10 mm) and multiple calculi came out to be highly significantly associated with GB carcinoma. Hence, screening via ultrasound and guided FNAC is proposed for females over 40 years of age with multiple small calculi not undergoing immediate cholecystectomy to detect early emergence of carcinoma. We also suggest to urge the clinicians to post patients with multiple, small GB calculi for cholecystectomy on a priority basis and histopathology should be done in each case of GB wall thickening (or cholecystectomy).

Limitation(s)

The main limitation of the study was that the predisposing factors for GB cancer other than gall stones were not ruled out from study population. Also, the present study was a single centre study. Further studies with a larger sample size should be conducted.

CONCLUSION(S)

The GB carcinoma along with cholelithiasis is present mostly in 5th to 7th decades of age groups with a preponderance of female gender. Presence of small, multiple GB calculi are highly significantly associated with GB carcinoma. The authors propose ultrasonography screening for females over 40 years of age with multiple small calculi to detect early carcinoma. They also suggest to urge the clinicians to consider patients with multiple, small GB calculi for cholecystectomy and histopathology.

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