

ORIGINAL ARTICLE

A clinicopathological study of nine cases of gallbladder carcinoma in 1122 cholecystectomies in Johor, Malaysia

Joon Joon KHOO *MBBS, MPath*, and NURUL Akmar Misron *MBBS**

*Monash University, Johor Bahru and *Department of Pathology, Sultanah Aminah Hospital, Johor Bahru, Malaysia.*

Abstract

An audit of 1122 cholecystectomies for a 6-year period from 2000 to 2005 was done to review cases of primary carcinoma of gallbladder. There were nine cases of primary carcinoma of gallbladder. Six were females and 3 males. Their ages ranged from 27 to 81 years. Pre-operatively, only 2 (11.1%) were clinically suspected of carcinoma while 3 were diagnosed as cholecystitis, two as cholelithiasis and one case each of ovarian cyst and intestinal obstruction. Intra-operatively, an additional four cases were suspected as gallbladder carcinoma with the remaining three cases diagnosed as only having gallstones. Altogether only 5 (55.6 %) cases were associated with gallstones. Six (66.67%) cases of gallbladder carcinoma had abnormal macroscopical lesions noted; either papillary lesions or polypoid masses. The remaining 3 cases had thickening of the wall, consistent with chronic cholecystitis. Seven cases were found histologically to be adenocarcinoma. Of these, two were papillary carcinoma and one signet ring cell type adenocarcinoma. One case of squamous cell carcinoma and one case of adenosquamous carcinoma were noted. This study highlights the importance of careful macroscopical and microscopical evaluation of a routine pathological examination of gallbladder removed for cholecystitis or cholelithiasis. It provides the incidence of gallbladder carcinoma in patients who underwent cholecystectomies in a government hospital in Johor, Malaysia.

Keywords: cholecystectomy, cholelithiasis, gall bladder carcinoma

INTRODUCTION

The incidence of gallbladder carcinoma (GBC) varies in different parts of the world.¹ It is an aggressive tumour with poor prognosis^{2,3,4} and early diagnosis is rarely achieved due to lack of symptoms and physical signs. We reviewed all cholecystectomies received in a Department of Pathology of a tertiary Hospital in Johor, Malaysia over a six-year period, and studied the cases of gallbladder carcinoma diagnosed on histopathological examination to determine the incidence and presentation of gallbladder carcinoma and its pathological features.

MATERIALS AND METHODS

A retrospective study was done on all cholecystectomies performed from 2000 to 2005 in Hospital Sultanah Aminah, Johor Bahru, Malaysia. The histopathological diagnoses for all gallbladder specimens received in its Department

of Pathology were noted. All cases diagnosed as primary gallbladder carcinoma were evaluated. The histopathological report with description of gross appearance of the gallbladder together with the Haematoxylin and eosin stained slides were reviewed. The surgical case notes including the preoperative entry, the operating notes and all clinical information of the patients were studied. The patients were traced to the surgical clinic or where necessary to the National Registry of Identification at the time of writing.

RESULTS

A total of 1122 cholecystectomies were received for the study period of 6 years. The age distribution of the patients was as noted in Figure 1. There were more females undergoing cholecystectomies than male patients with a male to female ratio of 1:2.16. The majority of patients (96.8%) had cholecystitis or cholelithiasis. A total of 9 patients,

six females and three males, were diagnosed to have GBC by histopathological examination. The male to female was 1:2. They were between the ages of 27 to 81 years old. The mean age was 56.7 years. Only two out of nine cases were clinically suspected to have GBC although all had preoperative ultrasound imaging. Three cases were clinically misdiagnosed as acute or chronic cholecystitis, two as cholelithiasis and one case each as intestinal obstruction and ovarian cyst. However, intraoperatively, four additional cases were suspected to be gallbladder carcinoma by the surgeon (Table 1).

The patients had varied symptoms that included pain in right hypochondrium (66.7%), anorexia (44.4%), nausea or vomiting (33.3%), weight loss (33.3%), pruritus (33.3%), fever (22.2%), malena or per rectum bleeding (11.1%), loose stools (11.1%) and malaise (11.1%). There was mass noted per abdomen in two cases (22.2%) and three cases (33.3%) had jaundice while one case (11.1%) had hepatomegaly.

Seven cases had either papillary or polypoid mass in the gallbladder while remaining three cases had only thickening of the wall. Five out of 9 cases (55.5%) were associated with gall stones, either single or multiple stones, while four cases were not associated with gall stones.

Majority of the tumours were adenocarcinoma (77.8%), of which two were papillary adenocarcinoma and one of signet ring cell type. There was one case each of squamous cell carcinoma and adenosquamous carcinoma noted (Figures 2a-e). The patient with adenosquamous carcinoma had focal areas of malignant squamous components (1/3 of the areas) in a predominantly malignant glandular background. There was also squamous metaplasia noted in the mucosal epithelium of the gallbladder in this patient.

The recently revised TNM classification system put together by the International Union Against Cancer and American Joint Committee on Cancer, was used in staging our patients in this study.⁵ The patients were staged based on the depth of the tumour infiltration, number of nodes involved and the presence of distant metastasis. One patient, who presented in stage IB, was lost to follow up. Of the remaining eight patients, six patients (75%) in varying stages at presentation had succumbed to their illness from two to 13 months after surgery, with a mean survival of seven months. Two other patients, both in stage IA, were still alive and on follow-up up to seven years after surgery.

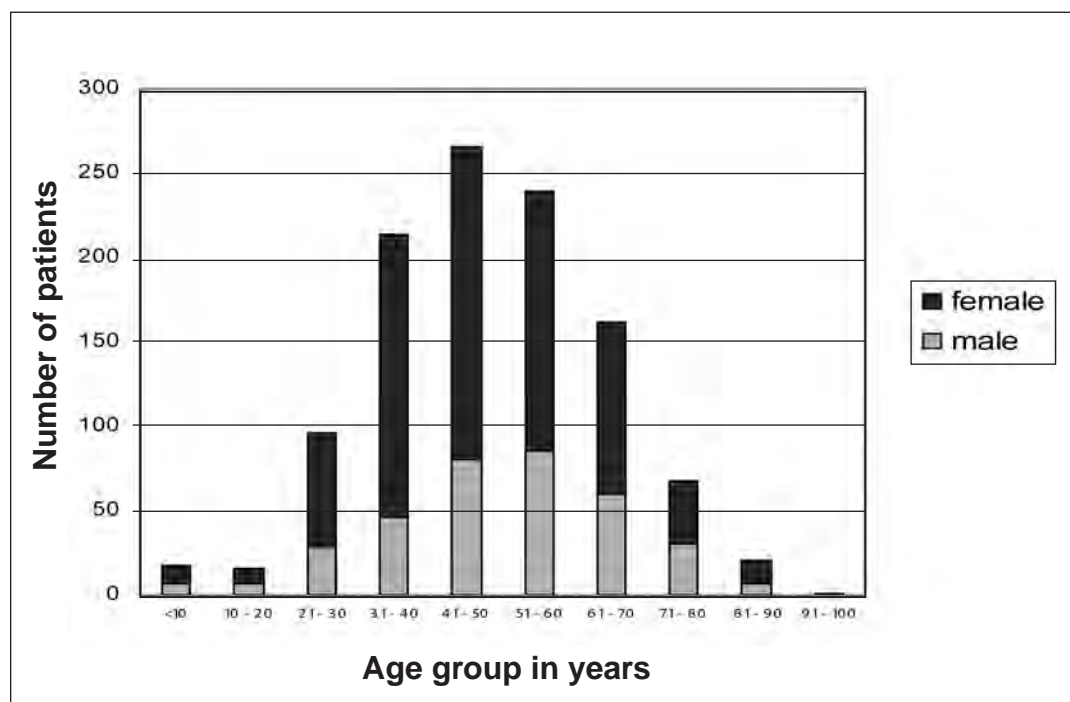


FIG. 1: Age and sex distribution of patients with cholecystectomy specimen (n = 1101)

TABLE 1: Characteristics of patients with gallbladder carcinoma (GBC)

No.	Age(yrs)/ Sex/Race	Pre-operative diagnosis of GBC	Intraoperative diagnosis of GBC	Type of operation	Macroscopical description	Lithiasis	Type of tumour	Stage ⁵	Status (survival in mths)
1.	43/F/Malay	No	No	Lap. Chole.	Papillary lesion	Yes (multiple)	Adenocarcinoma	T1N0M0 – Stage IA	Alive
2.	81/M/Malay	No	No	Open Chole.	Wall thickening	Yes (single)	Adenosquamous Ca.	T2N1M0 – Stage II	Died (5mths)
3.	66/F/Malay	Yes	Yes	Open Chole.	Polypoid mass	No	Papillary adenoca.	T1N0M0 –Stage IA	Alive
4.	74/M/Chinese	No	Yes	Laparotomy	Wall thickening	No	Signet ring Ca.	T3N9M1 –Stage IV	Died (4mths)
5.	70/F/Malay	No	Yes	Open Chole.	Polypoid mass	Yes (multiple)	Adenocarcinoma	T2N0M0 – Stage IB	Lost to f/up
6.	44/M/Malay	No	Yes	Open Chole.	Wall thickening	No	Squamous cell Ca.	T1N0M0 –Stage IA	Died (6mths)
7.	49/F/Indian	No	No	Open Chole.	Polypoid mass	Yes (multiple)	Adenocarcinoma	T2N1M0 – Stage II	Died (2mths)
8.	27/F/Malay	No	Yes	Laparotomy	Papillary lesion	No	Papillary adenoca.	T4N2M1 – Stage IV	Died (12mths)
9.	57/F/Malay	Yes	Yes	Open Chole.	Polypoid mass	Yes (multiple)	Adenocarcinoma	T2N0M0 –Stage IB	Died (13mths)

F=Female, M=Male, Ca= carcinoma, Adenoca.=adenocarcinoma

Lap. Chole. = Laparoscopic cholecystectomy, Open Chole. = Open Cholecystectomy

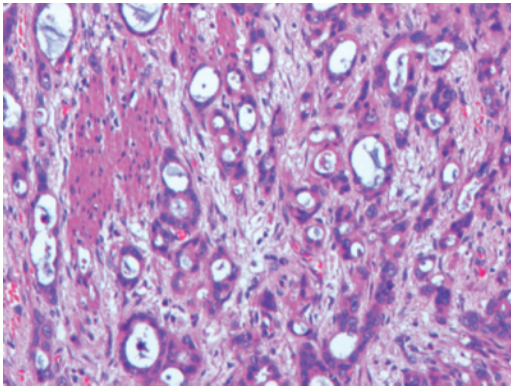


FIG. 2a: Adenocarcinoma. Malignant glands infiltrating the muscular wall of the gallbladder. (H & E, X 200)

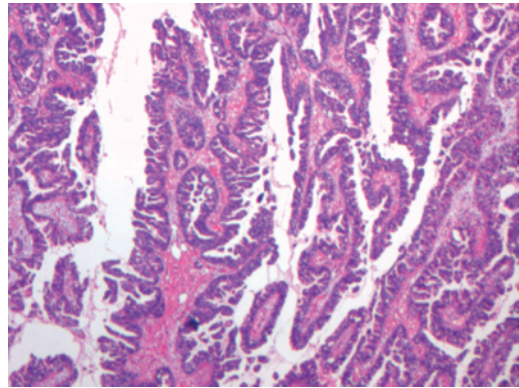


FIG. 2b: Papillary carcinoma. (H & E, X 200)

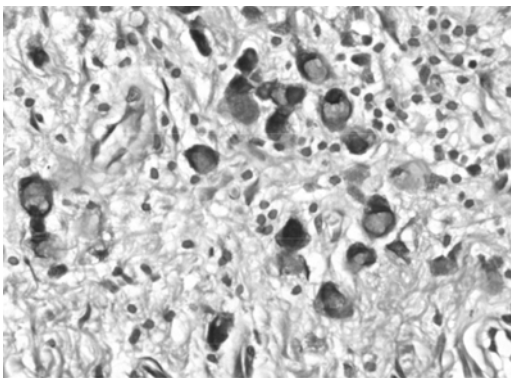


FIG. 2c: Signet ring cell carcinoma. Arrow points to the signet ring cells. (H & E, X 200)

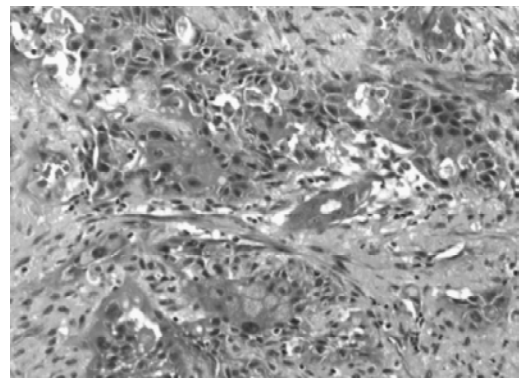


FIG. 2d: Adenosquamous carcinoma. Long arrow points to malignant squamous components and short arrow points to glandular components. (H & E, X 200)

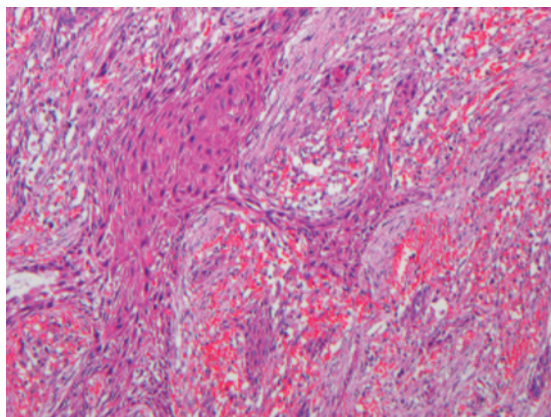


FIG. 2e: Squamous cell carcinoma. (H & E, X 200)

DISCUSSION

Primary malignancies of gallbladder are uncommon in Malaysia. The incidence is low compared to tumours of the gastrointestinal tract. Most times, the gallbladder is removed with the clinical diagnoses of cholelithiasis or cholecystitis. We evaluated 1122 cholecystectomy specimens and found only 9 cases of primary GBC (0.80%). The incidence of gallbladder carcinoma varies in different parts of the world. India, Chile and some parts of Japan reported a very high incidence of gallbladder carcinoma while other countries reported a lower incidence. For a 11-year period, the Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India⁶ reported 358 patients with GBC out of 2600 cholecystectomies performed in the same period (13.77%) while studies in other parts of the world reported an incidence as low as 0.38% to 1.15%^{7,8,9}. This is comparable with that of our study.

The clinical features of GBC included right hypochondrium pain, loss of appetite and weight, nausea and vomiting. These symptoms were non-specific and indistinguishable from gallstone disease. However, presence of jaundice, hepatomegaly and mass per abdomen may suggest the possibility of GBC. In our study only two cases were clinically suspected to have gallbladder carcinoma before operation. Thus, in 78% of the cases, malignancy was not clinically suspected.

Carcinoma of gallbladder may present as a mass or polypoid growth. It may also be local thickening of the wall as seen in three of our cases. This could be compatible with inflammatory changes of the gallbladder seen in gallstone disease. Hence, it was possible that in 33% of the cases, suspicion of malignancy was not evident despite gross examination of the gallbladder alone and hence, histopathological examination was required to make the final diagnosis. This makes selective approach to histopathological examination of gallbladder which was recommended by some studies^{7,10} unsafe and unjustifiable. Proper and careful examination of all gallbladder specimens including histopathological examination, regardless of the clinical diagnoses, is required at all times.

The mean age of patients with GBC in our study was 56.7 years and this was comparable with most other reported studies^{3,9,11} although in some studies it had been suggested that there was higher incidence of GBC with an older age.^{4,12}

Although the risk of GBC in patients with gallstones has been reported to increase a few fold^{13,14} and that gallstones were closely associated with GBC in many countries,^{15,16,17} our study showed that only 55.5% of GBC cases were associated with gall stones. This suggested that other possible aetiological factors could be implicated in our local context viz. genetic predisposition, chemical carcinogens, infections or dietary patterns that need to be studied on a larger scale.

Prognosis of patients with GBC and the survival depends largely on the extent of the disease (staging) and hence how early the patient is treated. However, early diagnosis is rarely achieved due to lack of specific symptoms and signs. This together with the poor therapeutic outcome for GBC makes survival of patients with gallbladder carcinoma dismal, as reported by many workers.^{4,18} This was also seen in our study where 6 out of 8 patients succumbed to the illness very rapidly after their presentation and diagnosis.

It had been shown that the histological type of the tumour also affected the prognosis. Henson et al⁴ in their study of GBC showed that papillary carcinoma were associated with the best survival, having a 5-year rate of 32%. They also showed that there was linear association between grade and survival. The number of our GBC cases was small and it was not possible to correlate the type of tumour histology and stage with the prognosis of the patients.

CONCLUSION

This study has highlighted the importance of proper histological examination of gallbladder specimens even when gallbladder carcinoma was not suspected upon clinical or macroscopic examination. GBC was not always associated with gallstones but may clinically mimic gallstone disease. Adenocarcinoma was the predominant histological type of GBC. It also showed that gallbladder carcinoma is a highly fatal disease but fortunately is not a common occurrence in our patients in Malaysia.

REFERENCES

1. Waterhouse J, Muir C, Correa P. Cancer Incidence in Five Continents, Vol 3. Lyon: IARC Scientific Publications, 1976.
2. Misra S, Chaturvedi A, Misra NC, Sharma ID. Carcinoma of the gallbladder. *Lancet Oncol* 2003; 4:167-76.

3. Batra Y, Pal S, Dutta U, et al. Gallbladder cancer in India: A dismal picture. *J Gastroenterol Hepatol* 2005;20:309-14.
4. Henson DE, Albores-Saavedra JA, Corle D. Carcinoma of gallbladder: Histologic types, Stage of disease, grade and survival rates. *Cancer* 1992;70:1493-7.
5. Sobin LH, Wittekind CH. Digestive system: gallbladder. In: *TNM classification of malignant tumours*, 6th edn. New York: Wiley –Liss, 2002; 84-6.
6. Kapoor VK. Incidental gallbladder cancer. *Am J Gastroenterol* 2001; 3:627-9.
7. Dix FP, Bruce IA, Krypczyk A, Ravi S. A selective approach to histopathology of the gallbladder is justifiable. *Surgeon*; 2003; 4:233-5.
8. Samad A. Gallbladder carcinoma in patients undergoing cholecystectomy for cholelithiasis. *J Pak Med Assoc* 2005;55:497-9.
9. Barcia JJ, Rodriguez A, Siri L, Masllorens A, Szwebel P, Acosta G. Gallbladder carcinoma in the “Hospital de Clinicas” of Uruguay: 1998-2002. A Clinicopathologic study of five cases in 802 Cholecstectomies. *Ann Diagn Pathol* 2004;8: 1-5.
10. Taylor HW, Huang JK. ‘Routine’ pathological examination of gallbladder is a futile exercise. *Br J Surg* 1998;85:208.
11. Kumar JR, Tewari M, Rai A, Sinha R, Mohapatra SC, Shukla HS. An objective assessment of demography of gallbladder Cancer. *J Surg Oncol* 2006; 93:610-4.
12. de la Cruz J, Hidalgo LA, Feliu J et al. Gallbladder adenocarcinoma: tumoural staging. Histological prognostic factors and survival. *Cir Esp* 2005;77:18-21.
13. Maram ES, Ludwig J, Kurland LT, et al. Carcinoma of the gallbladder and extrahepatic biliary ducts in Rochester, Minnesota. 1935-1971. *Am J Epidemiol* 1979;109:152-75.
14. Nervi F, Duarte I, Gomez G, et al. Frequency of gallbladder cancer in Chile, a high-risk area. *Int J Cancer* 1988;41:657-60.
15. Roa I, Ibacache G, Roa J, Araya J, De Aretxabala X, Munoz S. Gallstones and gallbladder cancer- volume and weight of gallstones are associated with gallbladder cancer; A case-control study. *J Surg Oncol* 2006;93:624-8.
16. Zatonski WA, Lowenfels AB, Boyle P, et al. Epidemiologic aspects of gallbladder cancer: A case-control study of the SEARCH Program of the International Agency for Research on Cancer. *J Natl Cancer Inst* 1997;89:1132-8.
17. Lowenfels AB, Walker AM, Althaus DP, et al. Gallstone growth, size, and risk of gallbladder cancer: An interracial study. *Int J Epidemiol* 1989;18:50-4.
18. Misra NC, Misra S, Chaturvedi A. Carcinoma gallbladder. In: Johnson CD, Taylor I (Eds). *Recent advances in surgery*, volume 20. London: Churchill Livingstone, 1997:69-87.