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Clinicopathological Spectrum Of Gallbladder Cancer In Kashmir – An Institutional Study

R. Makhdoomi¹, N. Bashir², N. Bhat³, S. bashir¹, F. Mustafa¹, A. Aiman¹, A. Charak¹, S. Hussain¹, S. Shafi¹, S. Bhat³, N. Bashir¹, Z. Zahir¹, P. Shah¹

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Abstract

Gallbladder cancer is a highly aggressive malignancy that usually presents at an advanced incurable stage. It is the fifth most common gastro-intestinal tumor and leads to approximately 2800 deaths in United States annually. This was a retrospective study carried out in the Department of Pathology, Sher–i–Kashmir Institute of Medical Sciences, a 650–bed super speciality hospital in Kashmir valley. We reviewed the histopathological records of all the patients who were diagnosed as carcinoma gallbladder from Dec 2009–Dec 2013. Gross findings and histopathological findings were noted from the departmental archival material and clinical records of the patients including the clinical presentation, laboratory investigations, radiological investigations, pre–operative diagnosis and intra–operative findings, were retrieved from the hospital records. We analyzed 57 cases of carcinoma gallbladder for their clinicopathological features. It included 19 males and 37 females. In our study, adenocarcinomas accounted for 87.5% of total carcinomas. Incidentally, all but one patient where gall stones were found, adenocarcinomas were seen. We have 4 patients of squamous cell carcinoma. In our series we have a single case of small cell carcinoma which was positive for neuroendocrine markers. In our study, gall stones were seen only in 8 cases (14%) of the total cases.

Key words

Gallbladder, Gallbladder cancer, Adenocarcinoma, Squamous cell carcinoma, small cell carcinoma, Gall stone

Aجريت دراسة استعادية في قسم الباثولوجيا ، معهد شريف–أ- كشير للعلوم الطبية ، وهي مستشفى فائقة التخصص ذو 650 سريرا في وادي كشير . قمنا بدراسة السجلات الباثولوجية النسيجية لجميع المرضى الذين تم تشخيصهم بالسرطانة المستعرضة في الفترة ما بين ديسمبر 2009 إلى ديسمبر 2013. تم تدوين الموجودات الباثولوجية النسيجية والملاحظات الخاصة من الملاحظات الأولية بالقسم والسجلات الإكلينيكية للمريض ، وقد شمل ذلك التجديدي الإكلينيكي ، الفحوصات الخُبرية ، الفحوصات الشعاعية ، التشخيص السابق للجراحة ، وملاحظات أثناء التدخل الجراحي وذلك من سجلات المستشفى . قمنا بتحليل 57 حالة مصابة بسرطان المرارة في كشمیر : دراسة مؤسسية

إن سرطان المرارة سرطان خبيث عدواني للغاية، غالبا ما في مرحلة متقدمة غير قابلة للشفاء ، وهو خاص أكثر أورام السبيل المعوي المعوي بصفة عام . ويشكل 14% من أولى حالات المرارة الباثولوجية النسيجية و الملاحظات الخاصة من الملاحظات الأولية بالقسم والسجلات الإكلينيكية للمريض ، وقد شمل ذلك التجديدي الإكلينيكي ، الفحوصات الخُبرية ، الفحوصات الشعاعية ، التشخيص السابق للجراحة ، وملاحظات أثناء التدخل الجراحي وذلك من سجلات المستشفى .

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Introduction

Gallbladder cancer is a highly aggressive malignancy that usually presents at an advanced incurable stage.\(^1\) It is the fifth most common gastro-intestinal tumor and leads to approximately 2800 deaths in United States annually.\(^2\) Although it is unusual in western countries, where the incidence rates range between 0.4 and 0.8 in men and between 0.6 and 1.4 in women per 100,000 population, high incidence rates up to 2–4 in men and 4–6 in women have been reported from various countries in Central and South America, Central and Eastern Europe and Japan.\(^3\) Various epidemiological reviews have reported that gallbladder cancer is not rare in Europe.\(^4\) The incidence of carcinoma gallbladder in India ranges from 1.01 per 100,000 for males to 10.1 per 100,000 for females,\(^5\) but the actual number may be much more in the endemic zones of western Bihar and eastern Uttar Pradesh, where it is the third most common malignancy of the alimentary tract.\(^6\) Gallbladder carcinoma is 3 times more common in women than in men.

The etiology of gallbladder cancer has been a source of speculation. The incidence of gallbladder cancer parallels the prevalence of gall stone disease; large and long standing gall stones being associated with the higher risk of gallbladder cancer.\(^8\) The risk of gallbladder cancer in patients with gall stones has been reported to have increased 4–7 times.\(^8\)

Patients and Methods

This was a retrospective study carried out in the department of Pathology, Sher-i-Kashmir Institute of Medical Sciences which is a 650-bed super speciality hospital. We reviewed the histopathological records of all the patients who were diagnosed as carcinoma gallbladder from Dec 2009–Dec 2013. Gross findings and histopathological findings were noted from the Departmental archival material and clinical records of the patients including the clinical presentation, laboratory investigations, radiological investigations, pre-operative diagnosis and intra-operative findings, were retrieved from the hospital records. The relevant blocks were retrieved and fresh sections were cut from the paraffin blocks and were analyzed by a single pathologist. Wherever appropriate, special stains and immunohistochemical stains were used.

Results

We analyzed 57 cases of carcinoma gallbladder for their clinicopathological features. The total neoplastic lesions in our study during this period were 60; 2 adenomas and one carcinoma in situ were excluded.

Our study included 19 males and 37 females. Females accounted for 66.1% of cases whereas males accounted for 33.9% of cases. The most common age group involved was 51–60 (38.5%) which had 22 cases. The youngest patient in our study was 25 years old and the oldest patient was 80 years of age. At the time of surgery, direct extension into liver was seen in 24 cases (42.8%). Pain abdomen was the most common symptom mostly localized to right hypochondrium and was seen in 65% cases. Some patients presented with fever, melena, dyspepsia and pain in epigastrium. 3 patients (5.2%) presented with jaundice and one
patient with cholangitis. Only one patient presented with right hypochondrial mass. In our study, fundus was the most common site (28%) where 16 patients showed tumor localized to fundus whereas in 14 patients (24.56%) the tumor was localized to body. Diffuse involvement of the gallbladder by the tumor was seen in 11 patients where it involved body and fundus or body and neck. In 9 patients the tumor was localized in the neck whereas the entire GB was involved in 9 patients (15.7%). In our study only 8 patients (14.2%) have concomitant calculi which included 7 cases of adenocarcinoma and one case of small cell neuroendocrine carcinoma.

The tumor size on gross and histology varied from < 1cm to 8cm. Most cases were seen in the size range of 3–4 cm. The type of tumors seen on histology are shown in Table 1. Nodal metastases were seen in 7 cases (12.2%) , and metastases to other sites like omentum, liver and colon were seen in 5 cases (8.9%). Most cases showed tumor infiltration into the serosa and others were restricted to muscle. There was no case of intra mucosal carcinoma in our study. Pre-operative CECT was available in 6 cases, 4 cases suggestive of GB mass, one showing a stricture and another documenting a dilated CBD with intra hepatic biliary mass and a thickened GB wall. Pre-operative CT was available in 10 cases, 6 cases showing GB mass and others showing features of obstructive biliopathy and a single case showing hepatolithiasis, cholelithiasis and choledocolithiasis. Ultrasonography was available in all but two patients and in 40 patients were suggestive of GB mass and in four patients suggestive of cholelithiasis; others showed non–specific features like thickening of gallbladder etc.

### Discussion

Primary carcinoma of gallbladder is an uncommon malignancy with a distinctive demographic and geographic distribution. In the United States, it is the sixth common gastrointestinal malignancy. The incidence of gallbladder cancer varies widely within India. Gallbladder cancer is much more common especially in women, in north and central India than in the west and south. Kashmir is a geographically and culturally distinct region in the northern Himalayas and the pattern of cancer varies from rest of India. In an analysis of various cancers from Kashmir, gallbladder cancer was found to have a percentage prevalence of 2.2% with a female preponderance. The carcinoma gallbladder has been reported to be common in Kashmiri females possibly because of high prevalence of gall stones. (11, 12)

We analyzed the clinicopathological pattern of 57 cases of gallbladder cancer in a tertiary care centre and our observations threw light on a few aspects

<table>
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<th>Pattern</th>
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<tr>
<td>Total No. of patients</td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>No. of PHL lesions</td>
<td>Multiple</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Solitary</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Diffuse</td>
<td>1</td>
</tr>
<tr>
<td>Non–contrast density</td>
<td>Hypodense</td>
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</tr>
<tr>
<td></td>
<td>Isodense</td>
<td>2</td>
</tr>
<tr>
<td>Pattern of enhancement</td>
<td>Gradual progressive enhancement</td>
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</tr>
<tr>
<td></td>
<td>Isodense in arterial phase</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Enhanced in portal phase</td>
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<tr>
<td></td>
<td>Washout in delayed phase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non–enhanced</td>
<td>13</td>
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**Table 1. Histopathological types of Gallbladder cancer**

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81
of the disease distinct to our valley. In our analysis of 56 patients, females outnumbered males and constituted 66% of total cases with a male to female ratio of 1:1.9. This finding was consistent with other studies where the male to female ratio was in favor of females however it was less than other studies with most series reporting a ratio of 1:3, 1:2.5, 1:4 (6,13,14,15). However Liang (16) reported a male to female ratio of 1:1. However, although women are two to six times more commonly affected by gallbladder cancer than men, the incidence steadily rises with age (17).

The most common presenting symptom in our series was abdominal pain (80%) followed by jaundice (10%), vomiting and nausea (10%), weight loss (6%); 4% patients presented with right hypochondrial mass. One of our patients presented with fever and another one presented with cholangitis. This is consistent with results from other studies which have reported abdominal pain to be the most common presenting symptom (14). Gallbladder cancer remains asymptomatic for a long time or presents with non-specific symptoms (6).

Anemia was a consistent feature seen in 76% of patients. Alkaline phosphatase was increased in 70% of the patients. CECT/CT was available in 16 cases and in all cases the findings were suggestive of a mass in gallbladder. Ultrasound was available in all but two patients and was suggestive of a mass in 80%. In one case it was suggestive of emphysema and another showed a solitary calculus. In 7 cases there were no feature of a gallbladder mass or a gallbladder pathology. There were incidence seen in 24 cases (42.8%). Gross features of the tumor are shown in Table 1 where the involvement of fundus is present in most cases followed by involvement of body. Entire gallbladder was involved in 9 cases. Metastases to omentum, liver and colon were seen in 5 cases and metastasis to nodes were seen in 7 cases.

Anemia, hyperbilirubinemia and elevated alkaline phosphatase have been a consistent finding in other studies (6,16). CT is better than ultrasound in detecting the gallbladder lesion (8) and helpful to know the status of liver involvement but of little value in knowing the nodal status (8). Consistent with our study, CT could not comment on nodal status.

Image guided FNAC was done in 10 patients and it was positive for malignancy in 6 patients. In 2 patients

Figure 1a. Gross appearance of a papillary adenocarcinoma of gallbladder

Figure 1b. Gross appearance of a tumor involving entire gallbladder
the material was inadequate and 1 patient showed acute inflammatory infiltrate. SKIMS, an institution in India, is a pioneer in introducing USG guided FNAC in gallbladder lesion and the results have shown a high sensitivity of guided FNAC (18).

In our study, gall stones were seen in 8 cases (14%) of the cases. Cholelithiasis is a well-established risk factor for the development of gallbladder carcinoma (19) and gall stones are present in 74% – 92% of affected patients (8,20). However in our study, gall stones were seen only in 14.28% of cases with carcinoma gallbladder. This is a significant finding in an area where gall stones have a high prevalence (21).

In view of the fact that few of our patients have associated gall stones, other possible etiological factors like infection exposure to chemicals etc. need to be taken into consideration.

Gallbladder cancers are epithelial in origin and account for 98% of all gallbladder malignancies (7). Adenocarcinomas account for 90% of gallbladder cancers and are characterized by glands lined
by cuboidal or columnar cells which may contain mucin. They may be well differentiated, moderately differentiated or poorly differentiated depending on the degree of gland formation (7). Several histological patterns of adenocarcinoma are recognized, papillary intestinal, mucinous (Fig.2d), signet ring or clear cell (7) (Fig.2a). Consistent with our study, adenocarcinomas accounted for 87.5% of total carcinomas. Incidentally, all but one patient where gall stones were found, adenocarcinomas were seen.

We have 4 patients with squamous cell carcinoma. The pure squamous cell carcinoma constitutes only 1% of all malignant gallbladder tumors and consists of cords islands or sheets of malignant squamous cell separated by dense fibrous stroma. These tumors most likely arise in the areas of previous squamous metaplasia, and their histologic features may vary from anaplastic to well differentiated, keratinizing squamous cell carcinoma (22). (Fig.2b)

The foci of squamous differentiation can be seen in gallbladder tumors and can vary in amount from very minimal to extensive. An arbitrary cut off <25% is used for adenocarcinomas with focal squamous differentiation and an adenosquamous carcinoma is labeled if the squamous differentiation varies from 25–99% (23). In an analysis of 34 cases of squamous and adenosquamous carcinoma, Rao JC (23) found the incidence of pure squamous carcinoma to be 1% and that of adeno–squamous carcinoma to be 4% but it was reverse in our analysis where adeno–squamous carcinomas of gallbladder have worse prognosis than ordinary adenocarcinomas.

Small (oat) cell carcinomas of the gallbladder are rare and highly aggressive tumors. They are histologically identical to small cell carcinomas of the lung and gastrointestinal tract. Paraneoplastic syndromes may be associated with small cell carcinoma of gallbladder (8,24). In our series we had a single case of small cell carcinoma which was positive for neuroendocrine markers. (Fig.2c)

Undifferentiated spindle cell carcinoma is a rare gallbladder cancer with a worse prognosis. Our study also saw a patient with undifferentiated spindle cell carcinoma which comprised of a mixture of sarcomatous and carcinomatous elements. The tumor exhibited a biphasic pattern on hematoxylin and eosin, but it exhibited a poor protein expression with sarcoma markers. There was focal reactivity for vimentin and a strong reactivity for vimentin and a strong reactivity for CEA (carcinoembryonic antigen) and CK (cytokeratin). According to WHO classification of gastrointestinal tumors, four variants of undifferentiated carcinoma of gallbladder are recognized out of which spindle cell and giant cell type are the most common (25). The pathogenesis of this tumor is not clear.

We have 10 incidental cases, the diagnosis of malignancy was not made at preoperative radiography and where cholecystectomy was done for some other indication. Incidental gallbladder cancer is found in up to 1% of cholecystectomy specimens for gall stone disease (26).

**Conclusion**

Gallbladder cancer is an unusual cancer more commonly seen in females. Adenocarcinoma is the most common histological type. Gall stones may not be necessarily associated with gallbladder cancer.

**References**


