

Incidental precancerous and cancerous neoplasms in routine cholecystectomy specimens – A fascinating series of cases in a tertiary care center



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ABSTRACT

Laparoscopic cholecystectomy is one of the most commonly performed surgeries for benign gall bladder pathologies. Pre-cancerous and malignant gall bladder neoplasms often have overlapping non-specific clinical manifestation in their early stages. Radiological findings are also non-specific in the early stages with the presence of cholelithiasis in a significant proportion of cases. Cholelithiasis is said to be one of the important comorbid risk factors for gall bladder carcinoma (GBC) as a source of constant irritation to biliary mucosa. In such cases, cholecystectomy done for benign indications may lead to a histopathological diagnosis of incidental gall bladder carcinomas. Pancreaticobiliary type of adenocarcinoma is the most common subtype of GBC with two described cases in this series. Invasive foci need to be ruled out in. All cases of high-grade biliary intraepithelial neoplasia as were seen in the third case. Intracholecystic papillary neoplasm is a recently described entity with one reported case in this series that was associated with invasive adenocarcinoma. Signet ring adenocarcinoma is a rarely encountered adenocarcinoma in gall bladder with worse outcome. One such case has been described here where the patient has succumbed to death within 3 months of surgery and during the course of adjuvant therapy.

Key words: Biliary intraepithelial neoplasia; Cholelithiasis; Incidental gall bladder carcinoma; Intracholecystic papillary neoplasm; Laparoscopic cholecystectomy

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INTRODUCTION

Laparoscopic cholecystectomy (LC) is one of the most common surgeries in today's scenario, gallstone disease with acute or chronic cholecystitis being the most common indication. LC performed for benign gall bladder pathologies may unexpectedly result in diagnosis of a malignant neoplasm. The rate of such incidence is 0.2–3.3%^{1,2} across various centers in the world. The gall bladder is one of the most common cancers in biliary tract, with a worldwide incidence of 0.3–1.5%,³ and reported incidence in India being 0.8–1%.⁴ In a vast majority of these cases, around 70–80%, there was the presence of

gall stones, where the latter have shown to increase risk of malignancy by 4–7 times.⁵ Gall bladder neoplasm may have a very silent and incipient presentation, with overlapping features of chronic cholecystitis, and may often be missed in radiology.⁶ Histopathology serves as the gold standard in these cases, which offers the final diagnosis.

This case series depicts five such cases of gall bladder neoplasms, where there was no pre-surgical clinical or radiological suspicion of any neoplastic pathology. All these cases have been diagnosed within a short span of 3 months. The aims of this study were to describe some pre-cancerous and malignant pathology in routine

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gall bladder specimens, their gross features, along with ancillary investigations. Second, it was to assess the clinical implications of these cases during post-operative follow-up and their management.

CASE SERIES

Case 1

A 55-year-old woman presented with occasional right hypochondriac pain for the past 6 months. Her ultrasonographic (USG) scan showed echogenic foci with posterior acoustic shadowing, indicative of cholelithiasis. She was planned for routine LC and specimen sent for histopathological examination.

The specimen measured 7 cm in length, bile-stained mucosa, and unremarkable serosa, with wall thickness of 4 mm and few fragmented gall stones. No area of proliferative growth or firm-to-hard area was seen on macroscopic examination of the specimen. Sections were submitted from the neck and body of gall bladder. Section from the body showed infiltrating dysplastic glands up to peri-muscular connective tissue in a microscopic focus of 5 mm, with pyloric and intestinal-type metaplasia in the neck resection margin (Figure 1). A focus of perineural invasion was also seen (Figure 2). The final diagnosis was well-differentiated (G1) adenocarcinoma, biliary type, pT2NxMx, in a background of pyloric, and intestinal metaplasia with chronic cholecystitis.

The patient was then referred to the medical oncologist, who advised a magnetic resonance imaging (MRI) scan to look for any hepatic or lymphatic or any distant metastasis which came out to be negative. She was put on chemotherapy and was doing well 4 months in the follow-up period.

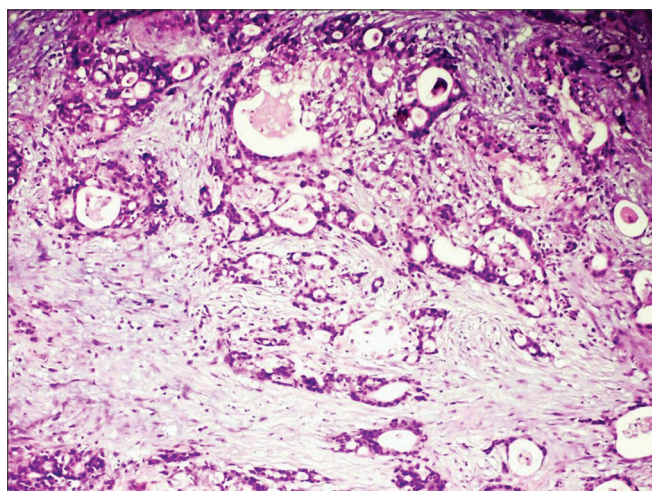


Figure 1: Infiltrating well-formed dysplastic glands in well-differentiated adenocarcinoma, biliary type (x100 magnification, Hematoxylin, and Eosin)

Case 2

A 60-year-old man presented with intermittent colicky pain in the right hypochondrium over the past 4 months, aggravated after intake of fatty meals. His USG scan showed a thickened wall of gall bladder (wall thickness=0.5 mm) with fibrosis and multiple small calculi, favoring Chronic cholecystitis with cholelithiasis. He was planned for LC and post-surgery; specimen was sent for routine histopathological examination.

The received specimen was 5 cm in length, brownish mucosa, focally congested serosa, wall thickness being 0.5 mm with few small stones in the lumen. No firm/abnormally thickened area was grossly palpable. Routine sections from neck and body of gall bladder were submitted for histopathological study. Section from the body showed microscopic foci (7 mm) of moderately formed glands infiltrating into muscular layer with uninvolved liver bed and neck resection margin (Figure 3). This was a case of early incidentally detected carcinoma with final diagnosis being moderately differentiated (G2) adenocarcinoma, biliary type, and pT1bNxMx.

Following the advice of the radiotherapy department, MRI scan done showed no metastasis or distant spread. The patient was advised regular follow-up visit only. Five-month post-surgery, the patient had been doing fairly well with no signs of recurrence/relapse.

Case 3

A 48-year-old woman presented with multiple episodes of acute right hypochondriac pain with radiation to the right shoulder and occasionally associated with nausea and

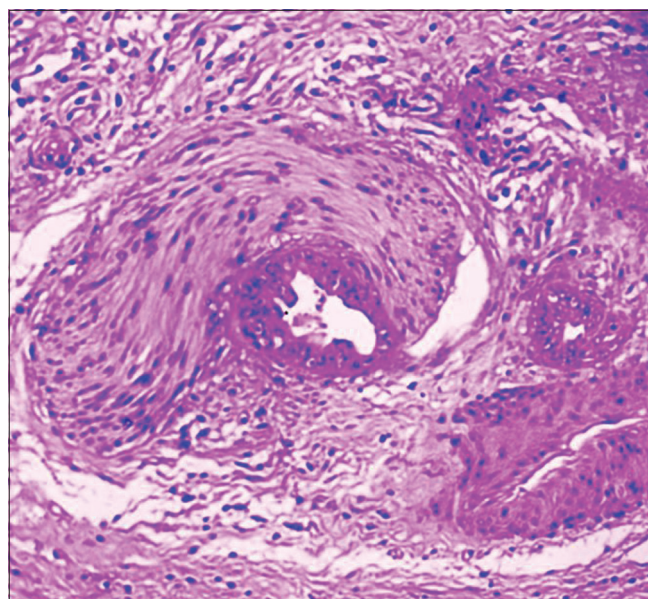


Figure 2: Perineural invasion in gall bladder adenocarcinoma (x400 magnification, Hematoxylin, and Eosin)

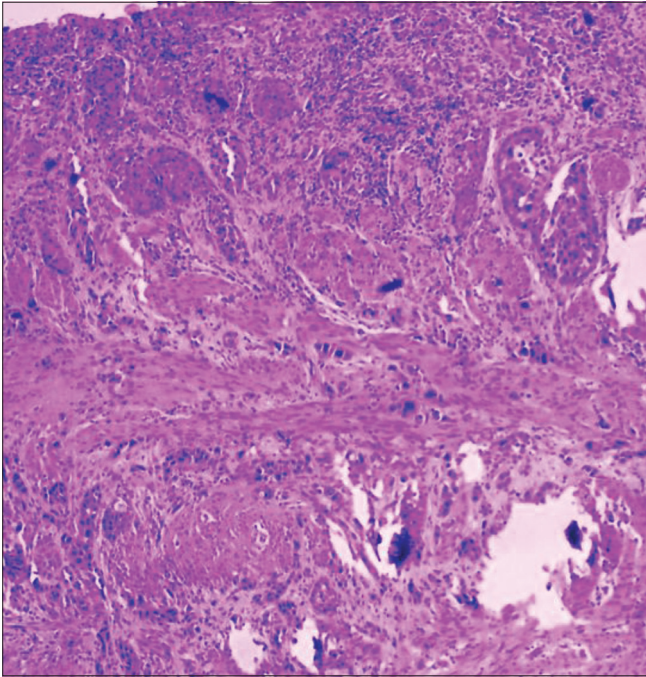


Figure 3: Infiltrating atypical glands in moderately differentiated adenocarcinoma, biliary type (×40 magnification, Hematoxylin, and Eosin)

decreased appetite. Her USG showed echogenic foci with posterior acoustic shadowing, indicative of cholelithiasis, and confirming the provisional clinical diagnosis.

Following routine LC, specimen was sent for histopathological examination in the Department of Pathology. Grossly, length of the gall bladder was 8.5 cm, wall thickness – 3 mm, mucosa – bile-stained, and serosa – unremarkable. In this case too, no firm/hard areas were seen and sections were submitted from the neck and body of the gall bladder. Hematoxylin and Eosin (H&E) stained sections showed marked mucosal dysplasia with nucleomegaly, pleomorphism, and stratification, loss of nuclear polarity, hyperchromasia, and atypical mitosis (Figure 4). No definite infiltration or desmoplastic stromal response was seen. Further sections were submitted to rule out any invasive foci. The final diagnosis was high-grade biliary intraepithelial neoplasia (BillN)/Carcinoma *in situ* (pTis NX MX).

The patient on being referred to oncology department was simply put on regular follow-up and was doing well for 7 months, as per the latest update.

Case 4

A 62-year-old female patient presented with recurrent right upper quadrant abdominal pain, along with anorexia, nausea, occasional low-grade fever associated with acute episodes of pain and jaundice for the past 2 months. Her ultrasound scan showed a small projection from the

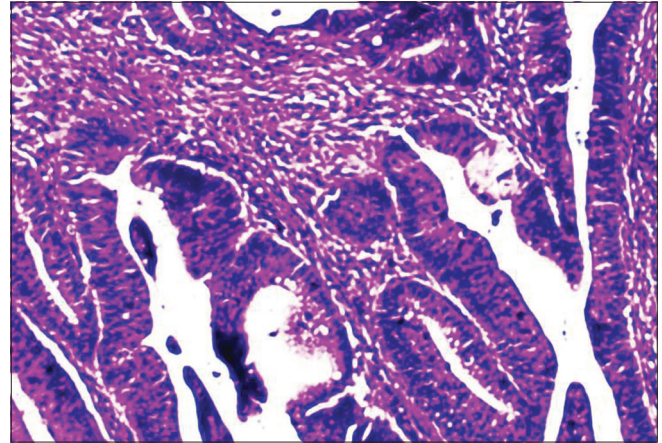


Figure 4: High grade BillN with nuclear stratification, hyperchromasia, loss of polarity and pleomorphism (×100 magnification, Hematoxylin, and Eosin)

gall bladder wall with increased vascularity, along with echogenic foci and posterior acoustic shadowing, and a diagnosis of gall bladder polyp with cholelithiasis was made.

Cut-open view of the received gall bladder specimen showed a papillary area in the fundus measuring 1.5 cm×1.5 cm with thickened and firm underlying wall, mucosa was brownish, serosa-focally congested, and the neck resection margin was grossly unremarkable. Multiple sections were submitted from neck, papillary areas of fundus, and adjacent unremarkable areas. H&E stained sections showed back-to-back dysplastic glands in papillary configuration (Figure 5) with areas of invasion up to perimuscular connective tissues (Figure 6). The neck resection margin, serosa, and cystic lymph node were free from tumor. The final diagnosis was intracholecystic papillary neoplasm with associated invasive adenocarcinoma, biliary phenotype, and pT2N0MX.

Her MRI scan showed no distant metastasis. She was put on a chemotherapeutic regimen and had shown no sign of relapse in 3-month follow-up period.

Case 5

A 69-year-old man presented with repeated episodes of diffuse abdominal pain with increasing tenderness on the right hypochondrium associated with nausea and decreased appetite. USG showed a contracted gall bladder with a wall thickness of 6mm, along with fibrosis and multiple small stones, favoring chronic cholecystitis with cholelithiasis.

Following LC, the specimen received in the Department of Pathology showed length of 6.5 cm, a maximum wall thickness is 7 mm, mucosa was brownish, serosa was congested. Again, no definitive growth or noticeably hard areas were seen in the wall. H&E sections showed infiltrating signet ring cells within the wall up to peri-

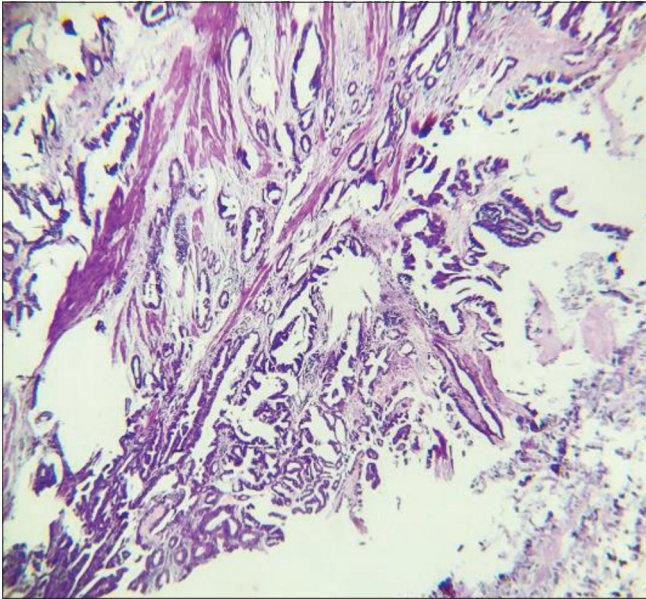


Figure 5: Papillary configuration in intracholecystic papillary neoplasm (×40 magnification, Hematoxylin, and Eosin)

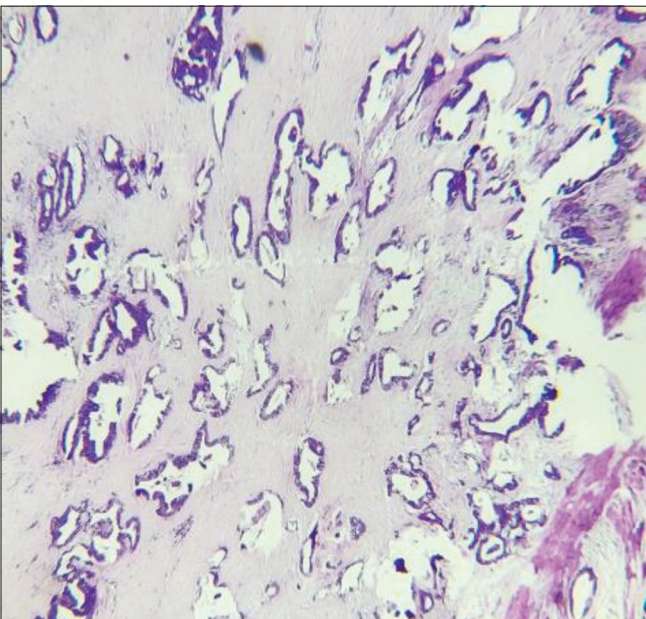


Figure 6: Associated invasive foci in intracholecystic papillary neoplasm (×40 magnification, Hematoxylin, and Eosin)

muscular connective tissues (Figure 7), close to the serosa and liver bed. A few areas in the wall showed pools of mucin with floating signet ring cells within it (Figure 8). The neck resection margin was free from tumor process. The final diagnosis was signet-ring cell carcinoma, pT2bNXMX.

MRI scan was unremarkable. The radiotherapist put him on adjuvant radiotherapy and chemotherapeutic regimen. However, the patient showed metastasis to liver within 3 months of follow-up and eventually succumbed to death.

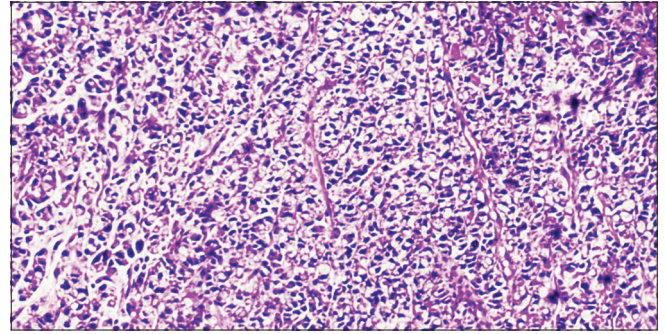


Figure 7: Sheets of signet ring cells in Signet ring cell carcinoma (Hematoxylin and Eosin, ×100 magnification)

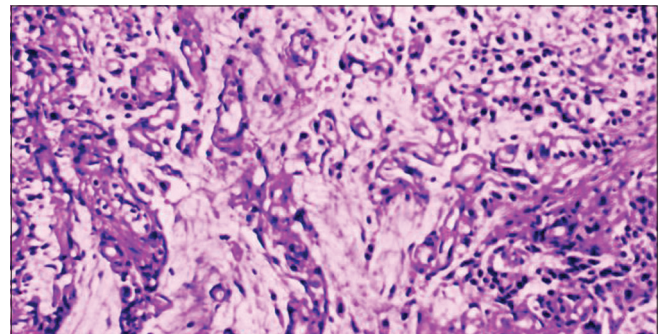


Figure 8: Mucin pools with floating signet ring cells in it (Hematoxylin and Eosin, ×100 magnification)

Details of all the above cases have been summarized below (Table 1).

DISCUSSION

Gall bladder carcinoma (GBC) is one of the most common malignancies of biliary tract and is the sixth most common malignancy of gastrointestinal tract.⁷ They are usually symptomatic at late stages with rapidly progressive disease and poor 5 year survival rate of <5% in advanced stage of the disease.⁸ Among the Indian subcontinent, North Indian women have shown a high incidence of this cancer.⁹ GBC in early stages may have clinical presentation of inflammation or due to associated cholelithiasis in terms of vague right hypochondriac pain, nausea, vomiting, low-grade fever, anorexia, or jaundice as were seen in the cases of this series. Patients often seek medical advice for these non-specific symptoms, with incidental diagnosis of early-stage carcinoma or pre-cancerous lesions.

Gall stones are seen to be associated with all cases in this study. Many studies have shown pathophysiologic role of cholelithiasis in neoplastic transformation of gall bladder. Cholelithiasis has been seen as major comorbid risk factors in 70%–98% GBC cases with an incidence of GBC related to cholelithiasis ranging from 0.3% to 12%.¹⁰⁻¹² Gall stones are said to irritate the biliary mucosa with injury and

Table 1: Summary of all the cases with respect to demography, clinical presentation, radiology, gross examination of specimens, histopathological findings, and long-term follow-up outcome

S. No.	Age (years)	Gender	Clinical presentation	Radiology	Gross examination of specimen	Microscopic findings	Follow-up
1.	55	Female	Occasional right hypochondriac for 6 months	USG-Echogenic foci with posterior acoustic shadowing (cholelithiasis)	Length: 7 cm, mucosa: bile-stained, serosa: unremarkable, wall thickness: 4 mm, few fragmented gall stones, no well-defined growth/firm-to-hard areas in the wall	Well-differentiated (G1) adenocarcinoma, biliary type, pT2NxMx, Neck resection margin-free, PNI- present	MRI-No metastatic foci, was put on chemotherapy, doing well in 4-month follow-up
2.	60	Male	Intermittent colicky pain in right hypochondrium for 4 months, aggravated after intake of fatty meals	USG-Thickened wall of gall bladder (wall thickness=0.5 mm) with fibrosis and multiple small calculi (Chronic cholecystitis with cholelithiasis)	Length: 5 cm, mucosa: brownish, serosa: focally congested, wall thickness: 5 mm, few small stones in the lumen. No firm/abnormally thickened area palpable	Moderately differentiated (G2) Adenocarcinoma, biliary type, pT1bNxMx, Neck resection margin, and liver bed-free	MRI-No metastatic foci, doing well in 5-month follow-up
3.	48	Female	Acute right hypochondriac pain with radiation to the right shoulder, nausea, and decreased appetite	USG-Echogenic foci with posterior acoustic shadowing (cholelithiasis)	Length-8.5 cm, wall thickness-3 mm, mucosa- bile-stained, serosa-unremarkable, no firm/hard areas were seen	High-grade biliary intraepithelial neoplasia (BillN)/ Carcinoma <i>in situ</i> (pTis NX MX)	Doing well in 7-month follow-up period
4.	62	Female	Recurrent right upper quadrant abdominal pain along with anorexia, nausea, occasional low grade fever associated with acute episodes of pain and jaundice for the past 2 months	USG-small projection from gall bladder wall with increased vascularity along with echogenic foci and posterior acoustic shadowing (gall bladder polyp with cholelithiasis)	Cut-open view-papillary area in the fundus (1.5 cm×1.5 cm), thickened and firm underlying wall, mucosa- brownish, serosa- focally congested, and neck resection margin was grossly unremarkable	Intracholecystic papillary neoplasm with associated Invasive adenocarcinoma, biliary phenotype, pT2N0MX	Receiving chemotherapy with uneventful 3-month follow-up period
5.	69	Male	Repeated episodes of diffuse abdominal pain with increasing tenderness on the right hypochondrium associated with nausea and decreased appetite	USG-contracted gall bladder, wall thickness of 6 mm, fibrosis, and multiple small stones (chronic cholecystitis with cholelithiasis)	Length-6.5 cm, wall thickness-7 mm, mucosa-brownish, serosa-congested, no definitive growth or noticeably hard areas in the wall.	Signet-ring cell carcinoma, pT2bNXMX	Put on adjuvant radiotherapy and chemotherapy. Showed signs of metastasis to liver within 3 months and eventually succumbed to death

PNI: Perineural invasion, USG: Ultrasonographic, MRI: Magnetic resonance imaging

inflammation followed by repair and this cycle of repeat leads to neoplastic transformation of biliary epithelium.⁶ This starts with dysplasia followed by carcinoma *in situ* and finally, leading to invasive adenocarcinoma.

As per Talreja et al., GBC usually presents in 6th–7th decade of life with 2–6 times more common among female population.¹³ Similar observation was also seen here where the age range was 48–69 years and female to male ratio

being 3:2. Female predominance can be explained by high level of estrogen, leading to cholesterol super-saturation in bile with increased propensity for cholelithiasis and associated GBCs.¹⁴

Ultrasonography is commonly the radiological investigation performed for gall bladder pathologies. This showed mainly non-specific benign findings like cholelithiasis and fibrosis-associated wall thickening. However, for the fourth case, a

polyp was suspected that later turned out to be ICPN. Thus, radiology was not helpful in these cases of incidental GBC as was also observed by Saavedra et al.¹⁵ Another pitfall of USG is Xanthogranulomatous cholecystitis that presents as marked thickening of wall with pseudotumoral infiltrate and may radiologically simulate GBC.¹⁶

Very characteristically, gross examination of the specimens was unremarkable in four cases of the series. There was no proliferative well-defined growth or abnormally hard and firm thickened wall in the specimens. The wall thickness varied between 3 mm and 7 mm and was thought to be associated with fibrosis and chronic inflammatory changes. Later, histopathology confirmed them as flat infiltrating type adenocarcinomas, as was also observed in some cases by Sujata et al.¹⁷ Fourth case, however, showed a papillary area in the fundus as a significant gross finding.

Histopathology serves as a gold standard for the diagnosis of incidental carcinomas as well as pre-cancerous pathologies. Pancreaticobiliary type adenocarcinomas are the most common subtype of gall bladder carcinomas accounting for 90–95% of all GB malignancies.¹⁸ This was also the histopathological variant identified in the first two cases of this series. Dysplasia of biliary mucosa is termed as BilIN and has two histologic grades – low and high. Identification of high-grade BilIN is important as it is often associated with microscopic foci of invasion, in approximately 80% of cases.¹⁹ Hence, the whole gall bladder needs to be sectioned and submitted in case of High-grade BilIN to exclusively rule out invasive adenocarcinoma. ICPN is a relatively newer concept of gall bladder neoplasm with very few reported cases in the literature.²⁰ ICPN with invasive component has been seen in 55% of cases and accompanying cholelithiasis in 20–22% cases.^{21,22} In this case of the series, both these associations were demonstrated. Signet ring cell carcinoma is a rare variant of adenocarcinoma primarily arising from gall bladder with limited reported cases available in the literature.²³ This is known to have a worse prognosis than conventional adenocarcinoma of the gall bladder.²⁴ Similar was the outcome in this series, where the patient developed liver metastasis followed by death within 3 months.

Treatment of gall bladder carcinoma is dependent on pathological staging of the disease. Precancerous lesions like high-grade BilIN/carcinoma – *in situ* requires watchful follow-up. Most of the incidentally detected adenocarcinomas are usually early gall bladder cancers that require follow-up visits only. Cases with higher-stage disease or involvement of margins may require extended cholecystectomy involving removal of a part of liver followed by adjuvant chemoradiation.

Limitations of the study

The study involved selective cases of GBC only spanning over a limited period of 3 months. Further study with a larger sample size and for greater duration may be undertaken to throw more light in this direction with a comparative analysis of benign gall bladder pathologies.

CONCLUSION

Gall bladder is one of the most commonly encountered specimen by reporting histopathologist. Very rarely, there may be incidental detection of pre-cancerous and frankly malignant gall bladder carcinomas. They may clinically and radiologically simulate benign gall bladder pathologies like cholelithiasis and often they are associated with gall stones as a major comorbid risk factor as well. Histopathology is the gold standard in diagnosis of these cases of incidental carcinomas, the majority being in the early stages. Thus, any case of biliary dysplasia must not go unnoticed and proper examination of the section is essential for detecting even a focal microscopic area of invasive carcinoma.

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DECLARATION OF PATIENT CONSENT

Written informed consent was obtained from the patients for publication of this manuscript and any accompanying images.

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