

## Extreme Rare Case of Primary Signet Ring Cell Carcinoma of Gall Bladder-Case Report

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### Abstract

Primary carcinoma of the gallbladder is an uncommon malignancy with a variable incidence. Women are affected generally than men (3-4:1) with higher incidence in increasing age. The signet ring cell sub type of adenocarcinoma is a rare and aggressive variant carrying worse prognosis. We report a case of primary signet ring cell carcinoma of gallbladder in a 55yr old woman. Ultrasound showed thickened gallbladder with multiple gallstones. Patient underwent open cholecystectomy. Grossly gallbladder was thickened with multiple stones. Histopathological examination revealed sheets of signet ring cells infiltrating full thickness of the wall. H&E, periodic acid-Schiff (PAS), Alcian blue & Cytokeratin 7 stains confirmed presence of signet ring cells. Post-op Endoscopy with biopsy was done to rule out primary in stomach. Early diagnosis and new lines of treatment in chemotherapy or new biological therapy should be encouraged to improve the survival and life quality.

**Keywords:** gallbladder, signet ring cell carcinoma

### 1. Introduction

Gallbladder carcinoma is the fifth most common malignant tumor of the gastrointestinal tract and the most frequent malignant neoplasm of the biliary tract. Most tumors (90%) are adenocarcinomas and the relative survival rate is low (14.5% at 5%) (Misra S., Chaturvedi, Misra, N. C., & Sharma, 2003; Donohue, Stewart, & Menck, 1998; Bazan et al., 2011). More frequent in females than males (3 to 4:1), over 90% of the patients are 50 years of age or older (Donohue et al., 1998; Pesic, Karanikolic, Djordjevic, Gmijovic, & Basic, 2002). The risk factors have not been determined yet, although a close relationship with gallstones has been described (Roa et al., 2006). Signet ring cell carcinoma is a rare and aggressive variant of mucinous adenocarcinoma. These tumours show a growth pattern (linitis plastica appearance) similar to that seen in gastric signet ring cell carcinoma (Murakata & Albores-Saavedra, 2004). It is also necessary to exclude benign signet ring change, sometimes occurring in the gallbladder, which is confined to the mucosa and does not infiltrate the wall.

### 2. Case History

55 year old woman presented with pain in the right hypochondrium since 3 months, vomiting since 15 days with no history of jaundice, diarrhea. All investigations were within normal limits. On ultrasound diffuse thickened gallbladder wall with f/o cholecystitis & multiple gallstones were seen. So the patient underwent an open cholecystectomy. Post-operative was uneventful. After histopathological diagnosis Upper GI Endoscopy with biopsy was done to rule out primary in stomach.

### 3. Pathological Findings

Gallbladder specimen was measuring 5.0×2.5 cm. External surface appeared to be unremarkable. On cut surface, the wall was thickened with a solid grey-white measuring 0.8 cm in maximum thickness. Multiple stones were identified in the lumen. The mucosa is velvety and appeared flattened at one place. Representative sections were taken including a section from the resection margin.

Microscopic examination revealed sheets of signet ring cells diffusely infiltrating the full thickness of the wall. In a few areas, small clusters of tumour cells were also seen. Nuclear atypia and mitosis were present. The

surface epithelium showed evidence of dysplasia. In periodic acid–Schiff (PAS), Alcian blue stains, the signet ring cells were seen to contain acid mucin in their lumina. Immunohistochemical stain Cytokeratin 7 was positive for signet ring cells. The gallbladder resection margin was focally involved by the tumor.



Figure 1. Gross Picture showing thickened GB wall with Gall stones

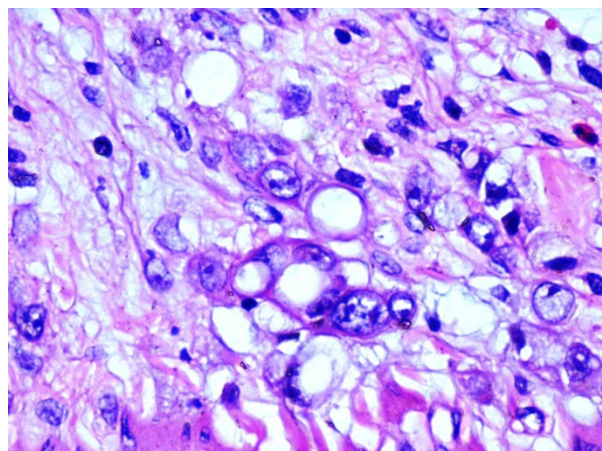


Figure 2. H&E stain(magnification x40)

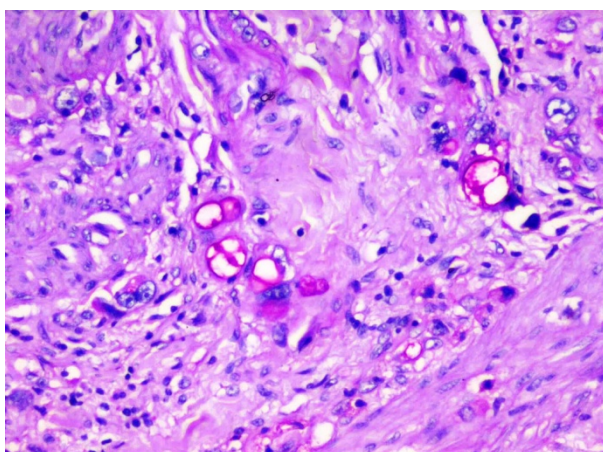


Figure 3. PAS Stain(magnification x40)

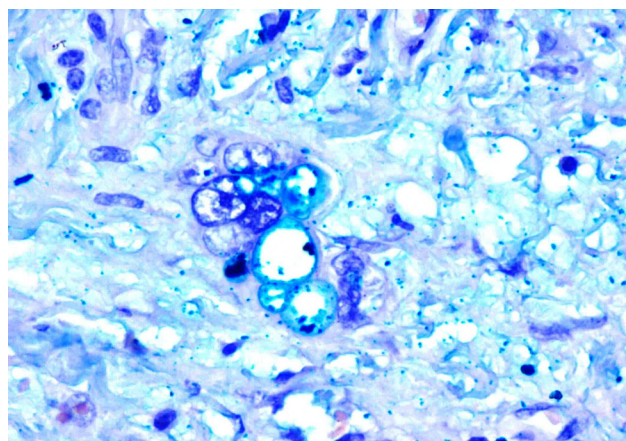


Figure 4. Alcian blue stain(magnification x40)

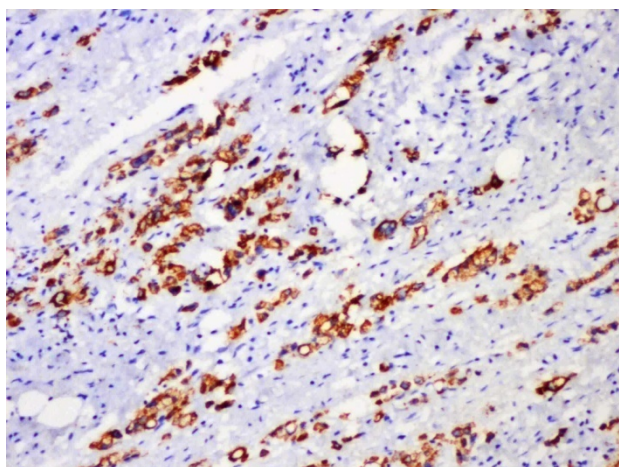


Figure 5. Cytokeratin 7 stain (magnification x20)

Patient required extended surgery with chemo and radiotherapy, which she refused.

#### 4. Discussion

Gallbladder carcinoma is the fifth most common malignant neoplasm of the digestive tract, adenocarcinoma being the most frequent histological type (Misra et al., 2003; Donohue et al., 1998; Bazan et al., 2011). Gallbladder carcinoma is more common in females than males and its incidence shows the tendency to increase with age (Donohue et al., 1998; Pesic et al., 2002). Gallstones is found to have a close relationship in development of gallbladder carcinoma. 10–25% of patients of gallbladder carcinoma do not have associated cholelithiasis (Roa et al., 2006; Singh, Ansari, & Narayan, 2012). A review of 1808 cases of gallbladder and bile duct cancers from California Tumor Registry noted a significant association between gallbladder carcinoma and occupational working automotive, rubber, wood furnishing, textile and metal fabricating industries (Paul, Rauf, & Branwood, 1980).

Gallbladder carcinoma may present as focal or diffuse asymmetric wall thickening in 20-30% cases. Gallbladder wall thickening differential diagnosis, including acute & chronic cholecystitis and adenomyomatosis, as well as diffuse hepatic or systemic diseases such as acute hepatitis, portal hypertension, and congestive heart failure (Van Breda Vriesman, Engelbrecht, Smithuis, & Puylaert, 2007).

The presence of signet ring cell proliferation in gallbladder which is a rare entity, accounts for a highly aggressive pathology. Signet ring cell carcinoma (SRCC) can arise from virtually any organ but most are from the stomach, breast, and colon (Bazan et al., 2011; Van Breda Vriesman et al., 2007). Regardless of the tissue origin, SRCCs frequently metastasize to peritoneal surfaces, regional lymphnodes, ovaries and lungs (Chu & Weiss, 2004; Karabulut, Yildirim, Abaci, Ilgici, & Ozyilkan, 2008; Panić, Marusić, & Mijić, 2010). Less commonly metastasis can be seen in small and large bowel, heart, kidney, ureters, diaphragm and omentum. Tetsyri reported a case of SRCC which over-expressed *c-myc oncogene* and that a specific monoclonal antibody with reactivity against gallbladder is being studied (Nishida et al., 1997). Immunohistochemical staining is useful to determine the origin and malignant potential of the signet ring cells. Gastric SRCC is positive for CK7, CK20. Breast and colon SRCC are mostly negative for CK7 and CK20 (Panić, Marusić, & Mijić, 2010). Our case showed CK7 positive, with CK20 negative results, thus confirming its malignancy and ruling out breast, colon and stomach as the SRCC origin.

Non neoplastic signet ring cells may be confused with SRCC. The lack of nuclear atypicality, hyperchromatism, admixture of histiocytes and other inflammatory cells favour signet ring change (non neoplastic) (Ragazzi, Carbonara, & Rossi, 2009; Suri et al., 2001). Nuclear atypia, mitotic figures, hyperchromatism and absence of inflammatory cell infiltration were seen in this case confirming the diagnosis of carcinoma.

In our case signet ring cells involved all the layers of gallbladder wall upto serosa but not serosa and beyond. The patient was in stage II (Edge et al., 2010).

Re-exploration to resect liver tissue near the gallbladder bed or extended or formal hepatectomy and lymphadenectomy including N1 and N2 lymph node basins may be associated with delayed recurrences or extended survival in patients with stage I or II gallbladder cancer. With the exception of some patients with focal stage IIA disease, these types of patients have cancer that cannot be completely resected. Because of its rarity, no specific clinical trials exist; however, such patients can be included in trials aimed at improving local control by combining radiation therapy with radiosensitizer drugs (Shirai, Yoshida, Tsukada, & Muto, 1992; Yamaguchi et al., 1997).

Open cholecystectomy was done in our patient without any suspicion of malignancy. After the confirmation of the nature of malignancy and stage, patient was advised for revised extended surgery with chemo and radiotherapy, but the patient refused.

#### 5. Conclusion

Primary carcinoma of the gallbladder is an unexpected histopathological finding in an elective cholecystectomy specimen done for benign gallbladder diseases. In spite of the modern diagnostic procedures, early diagnosis of gallbladder carcinoma is rare therefore a routine histopathological examination of all cholecystectomy specimens is a must. Histological type, grade and stage of the disease are the predictors of prognosis with highest postoperative survival in patients with early carcinoma and lowest in high grade and inoperable carcinoma. With only a few cases reported and an apparently ineffective classic line of treatment, we believe that more research about the biology of this cell line should be encouraged in order to modify the current chemotherapy or to add biological therapy.



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