

Linitis plastica like primary signet ring cell carcinoma of the gallbladder - an extremely rare variant

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Key words

Gallbladder • Signet ring cell carcinoma • Immunohistochemistry

Summary

Signet ring carcinoma (SRCC) of gallbladder is an extremely rare tumor accounting for approximately 3% of all gallbladder carcinomas, with a handful of case reports in the literature.

We report a case of signet ring cell carcinoma of the gallbladder in a 70 year-old female who was operated upon after the preoperative diagnosis of cholecystitis with cholelithiasis, based on ultrasonographic findings and subsequently diagnosed as signet ring cell carcinoma of the gallbladder on histopathological examination. Grossly there was no discrete growth, instead tumor presented as linitis plastica like diffuse thickening of the gallbladder wall. Microscopic examination revealed a diffusely infiltrative car-

cinoma comprised exclusively of signet ring cells and confirmed by periodic acid-Schiff (PAS), Alcian blue & Cytokeratin 7 stains. Post-operative clinico-radiological workup was done to exclude secondary. This highly aggressive signet ring cell carcinoma of gallbladder is being reported because of its rarity, its unique histomorphological features and diagnostic inadequacy of the routinely performed ultrasonography as well as highlighting the use of special stains and immunohistochemistry to exclude other possibilities. Our case highlights that routine histopathological examination of all the cholecystectomy specimens is a must to facilitate the early diagnosis of aggressive signet ring cell carcinoma gallbladder.

Introduction

Gallbladder carcinoma remains the commonest neoplasm affecting the biliary tract. Its incidence is significantly higher in females compared to males and its frequency further increases with increasing age. Cholelithiasis is the most common associated finding¹. Almost half of the cases are diagnosed at late stage where extensive spread renders it inoperable². Most of the gallbladder cancers are adenocarcinoma. Signet ring carcinoma (SRCC) of gallbladder is an extremely rare tumor accounting for approximately 3% of all gallbladder carcinomas³, with a handful of case reports in the literature^{1,2,4-14}. Japanese literature quotes its incidence as 1% of primary gallbladder carcinoma based on the autopsy finding². It is an aggressive variant of mucinous adenocarcinoma and carries worse prognosis⁴. Similar tumor type is known to occur in stomach, colon and breast. Metastasis from these sites to gallbladder may occur and it is necessary to exclude the secondary from these sites before labelling it as primary signet ring cell carcinoma of gallbladder. Immunohistochemistry is of great help in

determining the site of origin. Gallbladder carcinoma is regarded as highly aggressive malignancy and thus early detection and radical surgery is crucial for better clinical outcome⁴. An endeavour is made to document the extremely rare primary signet ring cell carcinoma and to contribute in the spectrum of gallbladder carcinoma. We report a case of signet ring cell carcinoma of the gallbladder in a 70 year-old female who was operated upon after the preoperative diagnosis of cholecystitis with cholelithiasis, based on ultrasonographic findings and subsequently diagnosed as signet ring cell carcinoma of the gallbladder on histopathological examination.

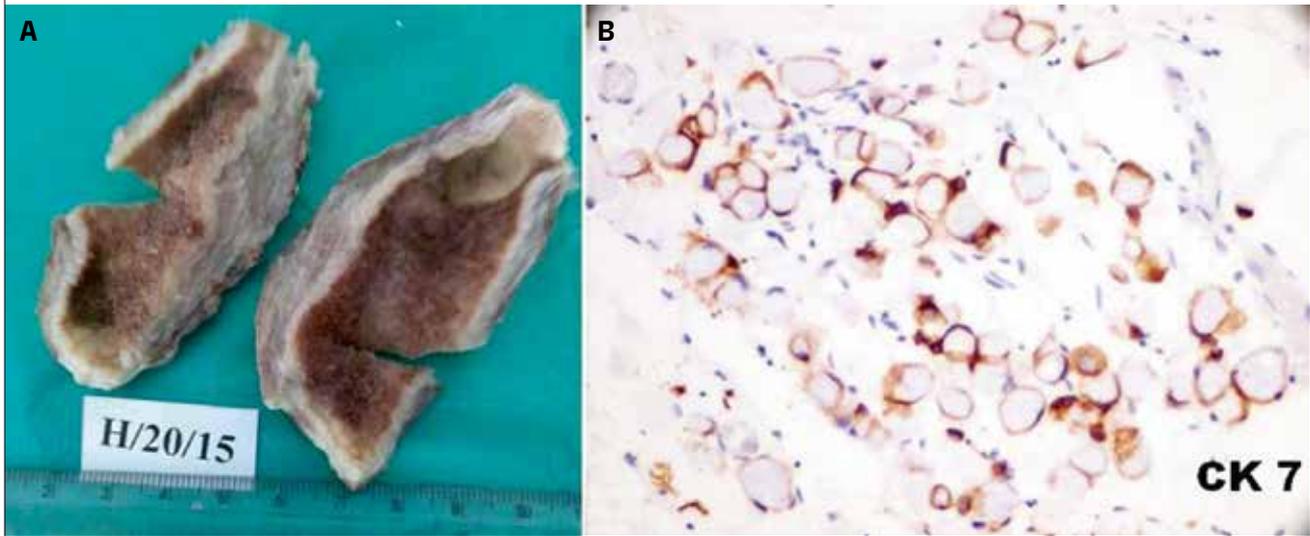
Case report

A 70 year old female patient presented with complaints of dull aching pain in right upper quadrant of the abdomen of 2 months duration. She also complained of loss of weight and appetite over past 6 months. On ultrasonography there was diffuse thickening of the gallbladder wall with multiple calculi. Hematological work up

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Fig. 1. (A) Gross photograph showing diffusely thickened gallbladder wall with focally ulcerated mucosa. (B) Signet ring cells showing Cyto-keratin 7 positivity (IHC, X400).



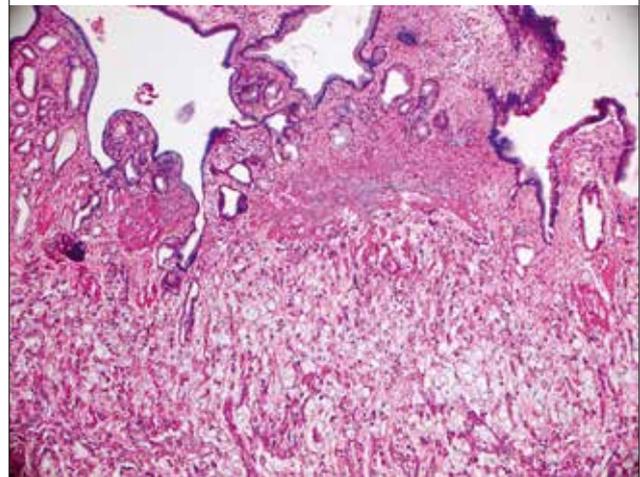
showed Hb- 10.5 gm/dl with normocytic normochromic anemia and mild leucocytosis (TLC- 12500 cells/mm³), rest all parameters were within normal limits. On biochemical examination total bilirubin was 1.6 mg/dl and S. ALP was 1024 (IU/L). She was taken up for open cholecystectomy after the preoperative diagnosis of cholecystitis and cholelithiasis, based on ultrasonographic findings; the specimen was sent for histopathology.

We received an already cut opened gallbladder of size 7.5x3x1.5 cm with multiple gallstones. Serosa was reddish brown in color. There was diffuse irregular thickening of the wall with few shiny mucoid areas. Wall thickness varied from 0.6 to 1.2 cm. Mucosa appeared focally ulcerated and no obvious growth was seen in the cavity (Fig. 1 A). Representative sections were taken including the section from the resected margins.

Microscopic examination revealed presence of signet ring cells diffusely infiltrating through all the layers of the gallbladder wall, invading up to the serosa (Fig. 2). The signet ring cell (large columnar to polygonal cells with a small round basal or eccentric nucleus and vacuolated cytoplasm) comprises of more than 90% of the tumor cell population (Fig. 3). These cells were present in diffuse sheets and also infiltrating singly. At places these cell were seen floating in the pools of extracellular mucin. Resected margin was involved by the tumor. Tumor cells were positive for periodic acid-Schiff (PAS), and Alcian Blue. On immunohistochemistry, tumor was positive for CK7 (Fig. 1 B) and negative for CK-20, ER, CDX2 and MUC2. The histopathological diagnosis of signet ring cell carcinoma of the gallbladder was conferred.

Further clinical and radiological workup was done to exclude secondary from breast, colon and gastric carcinoma and no evidence of malignancy at these sites was found.

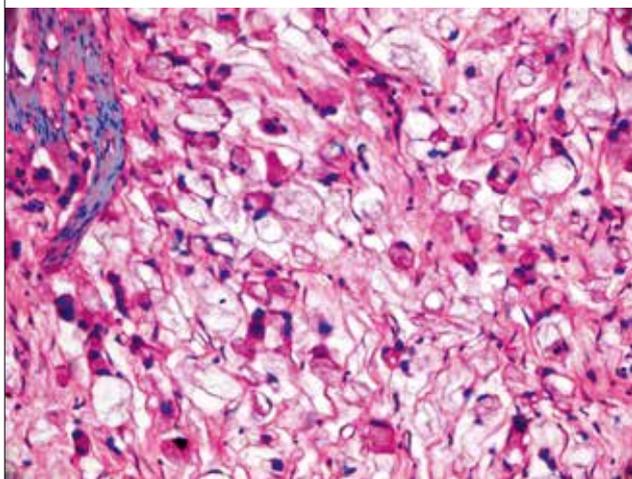
Fig. 2. Low power view showing sheets of signet ring cells diffusely infiltrating the gallbladder wall (Haematoxylin-Eosin stain, X100).



Discussion

Gallbladder carcinoma is reported to be the fifth commonest malignant neoplasm of the digestive tract⁴. It is the most common malignancy of the biliary tract with significant female preponderance and marked ethnic and geographical variation in different parts of the world¹⁵. It remains amongst the top most causes of cancer mortality in North India^{16 17}. Documented incidence of gallbladder carcinoma in North India is 21.5/100,000 females¹⁵. Its prevalence is three to five times higher in females and highest frequency is observed at 65 years of age with gall stone^{18 19 20}. Patients usually present with jaundice, nausea, vomiting, anorexia and abdominal pain. Clinical features overlap with those of benign gallbladder disease thus preventing its early detection and hence majority of

Fig. 3. High power view showing sheets of signet ring cells with cytoplasmic vacuolation and compressed eccentric nuclei (Haematoxylin-Eosin stain, X400).



cases are diagnosed at advanced stage which is associated with a poorer prognosis⁵.

Various risk factors associated with gallbladder carcinoma are cholelithiasis, porcelain gallbladder, cholecystoenteric fistula, adenomyomatosis, ulcerative colitis, anomalous pancreaticobiliary junction, chronic typhoid infection, xanthomatous cholecystitis and focal mucosal microcalcifications¹⁸. 60% to 90% of gallbladder carcinomas are associated with gall stones and particularly with cholesterol type however only 1-3 % of patients with gall stones develop gallbladder carcinoma^{18,19}. It has been reported that 10-25% of patients with gallbladder carcinoma do not have associated cholelithiasis²¹. Adenocarcinoma is the most common type of gallbladder carcinoma accounting for upto 90%. Gallbladder carcinoma is classified by WHO into various prognostically significant morphologic subtypes- intestinal, gastric foveolar, biliary mucinous, signet ring cell, clear cell and hepatoid variants³. Signet ring cell carcinoma is a rare type and account for only 3% of all gallbladder carcinomas³. It is an aggressive variant of mucinous adenocarcinoma with worse prognosis and frequent metastasis to regional lymph nodes, peritoneal surfaces, lung and bone^{14,6}. In a large cytology based Indian study on gallbladder carcinoma, the frequency of SRCC subtype was 0.5% (2/437) of all carcinomas¹⁵.

Gallbladder carcinoma may present as focal or diffuse asymmetric wall thickening in 20-30% cases. The differential diagnoses of gallbladder wall thickening includes, acute and chronic cholecystitis, and adenomyomatosis, as well as diffuse hepatic or systemic diseases such as acute hepatitis, portal hypertension, and congestive heart failure. Similar to gastric SRCC, the gallbladder SRCC exhibit linitis plastica like appearance and thus present as focal or diffuse asymmetric wall thickening^{3,7}. In our case also there was no discrete growth, instead tumor presented as linitis plastica like diffuse thickening of the wall. In several case reports well defined tumor mass

was present with or without wall thickening^{15,8,9}. Table I summarizes salient features of several case reports on SRCC gallbladder. In our case, primary signet ring cell carcinoma of gallbladder came as the histopathological surprise in an elective cholecystectomy specimen done for benign gallbladder disease. Our case highlights the significance of a thorough tissue sampling of all the cholecystectomy specimens to facilitate the early diagnosis of aggressive signet ring cell carcinoma gallbladder.

Signet ring cell carcinoma can arise from any organ but most are known to occur in stomach, colon and breast. Metastasis from these sites to gallbladder may occur and consequently it is necessary to exclude the secondary from these sites before labeling it as primary signet ring cell carcinoma of gallbladder. A panel of immunohistochemical markers involving CK7, CK20 and ER must be used to determine the site of origin and nature of these tumors. The usual immunohistochemistry pattern of gallbladder SRCC is CK7 positive, CK20 and ER negative. Gastric SRCC are CK7 and CK20 positive, colonic SRCC are CK7 and CK20 negative while breast SRCC are mostly CK7 and CK20 negative and ER positive. Our case showed CK7 positive, with CK20, ER, CDX2 and MUC2 negative results, thus confirming its malignancy and ruling out gastric, breast and colon as the SRCC origin. Documented immunohistochemical reactivity of SRCC of various sites is briefly mentioned in Table II.

Rarely non-neoplastic signet ring cell change may be seen in colonic and gallbladder mucosa and it should be considered in the differential diagnosis of signet ring cell carcinoma. It may lead to multilayering of the mucosa and may form intraluminal nests however it do not infiltrate beyond mucosa and may be seen admixed with inflammatory cells. They lack nuclear atypia, hyperchromasia or increased mitotic activity^{12,24,25}. Nuclear atypia, hyperchromasia, mitotic figures and absence of inflammatory cell infiltrates were seen in our case confirming the diagnosis of carcinoma.

Overall SRCC are regarded as highly malignant dedifferentiated adenocarcinomas which lack cell-cell interactions and are characterized by presence of large numbers of mucin filled vacuoles and intracytoplasmic lumina on electron microscopy¹. Yasuhisa Fukui postulated that there is activation of ErbB2/ErbB3 signaling pathway causing disruption of adherent junctions which leads to loss of cell-cell interactions and also enhances the cell growth. In addition activated phosphatidylinositol 3-kinase (PI3K) pathway causes increased mucin secretion and formation of signet ring carcinomas²². Nishida T established human gall-bladder cancer cell line (FU-GBC-2) in tissue culture that showed morphological characteristics of signet ring cells ultrastructurally and were positive for carcinoembryonic antigen, CA19-9 and epithelial membrane antigen, but negative for vimentin on immunocytochemistry²³.

Early diagnosis and treatment can significantly improve the prognosis and survival in patients with gallbladder carcinoma however; non specific and late appearance of

Tab. I. Summary of reported cases of signet ring cell carcinoma (SRCC) of gallbladder.

S. No	Authors	Year	Age/ Gender	Clinical Presentation	Gall stone	Gross	Metastasis/ extension into adjacent organ	Period of survival after diagnosis
1	Krunic AL et al ⁶	2007	38 years/ Male	No details available	No details available	No details available	Skin, scalp, perianal area and bone	20 months
2	Karabulut Z et al ⁸	2008	76- years/ Male	Nausea and dyspepsia. right upper quadrant pain.	Present	Tumor mass	Right colic flexure	Three months
3	Afroz N et al ¹⁰	2008	70 years/ male	Cholecystitis and cholelithiasis	Multiple stones	Thickened wall at the fundus	No details available	No details available
4	Minami Y et al ¹³	2009	68 years/ male	Epigastric pain and vomiting	-	Invasive papillary tumor at the gallbladder fundus	Metastasis to regional lymph nodes	2 years and 10 months
5	Mondal. S.K ⁵	2010	32 years/ Male	Right upper quadrant abdominal pain, anorexia and jaundice	Absent	Mass in the neck region	Celiac lymph node metastasis	Two months
6	Pavić I et al ¹¹	2010	86 years/ Female	Icterus and history of intermittent abdominal pain over the course of one year.	Present	Thickened wall with tumor in cystic duct	Liver metastasis	Postoperative day 4
7	Ahmad and Qureshi ¹²	2010	53 years/ Female	Pain in the right hypochondrium	Multiple stones (USG finding)	Diffusely thickened wall	No details available	No details available
8	Czyszczoń and Alatasi ¹⁴	2010	22-years/ Male	Nausea, vomiting, yellow sclera, right and left upper quadrant and epigastric pain	Absent	Thickened gall bladder wall and cystic duct	Invasion of bile duct and wall of the pyloric stomach.	Lost to follow-up
9	Bazan F et al ⁴	2011	63 years/ Male	Dull epigastric pain	Present	Empyema	Metastasis in the liver, lymph nodes, pleura, peritoneum and subcutaneous tissue.	Ten months
10	Pudasaini S et al ⁹	2011	70 years/ Female	Pain in the abdomen, bile stained vomiting and failure to pass urine.	Absent	Mass along with wall thickening	Retroperitoneum and mesenteric lymph node	20th post operative day
11	Ahmed GN et al ¹	2014	54 years/ Male	Upper abdominal pain and anorexia	Present	Polypoidal mass	None at the time of diagnosis	Under follow
12	Ohno Y et al ²	2014	71 years/ Male	Right upper abdominal pain and obstructive jaundice	No details available	Gallbladder was filled with mucus. Mucosa smooth	Pulmonary tumor thrombotic microangiopathy	Died due to acute pulmonary failure
13	Padhiari RK et al ⁷	2014	55 years/ Female	Pain in the right hypochondrium and vomiting	Multiple stones	Thickened wall	None at the time of diagnosis	No details available
14	Present case	2015	70 years/ Female	Pain in the right hypochondrium, loss of weight and appetite	Multiple stones	Diffusely thickened wall	None at the time of diagnosis	Lost to follow-up

Tab. II. Immunohistochemical reactivity of signet ring cell carcinoma (SRCC) of various sites

Tumor	CK7	CK20	CDX2	ER	MUC1	MUC2	p53
Gastric SRCC	+	-/+	-	-	-	+	+
Breast SRCC	+/-	-	-	+	+	-	+
Colon SRCC	-	+	+	-	-	+	+
Gall Bladder SRCC	+	+/-	-	-	+	-	+
Present case	+	-	-	-	Not done	-	Not done

the clinical symptoms delays the diagnosis to advanced stage and worsens the prognosis. Stage of gallbladder carcinoma has direct impact on patient survival. The expected 5 year survival for grade I patients is reported as 75-100% and reported mean survival of stage IV gall bladder carcinoma is 3.7 months⁹. Current therapeutic modalities being used to treat this deadly tumor, are wide resections and chemotherapy drugs such as cisplatin and 5-fluorouracil. Newer biological therapy such as monoclonal antibody c-myc oncogene, are also being studied to improve the survival and life quality of such patients⁴.

Signet ring cell carcinoma of gallbladder is a highly aggressive neoplasm with potential risk of visceral and bony metastasis; several cases with metastasis or extension into adjacent organ are on record^{4 5 6 8 9}. Available reports revealed the fact that patient mortality has occurred within one year despite the radical surgery and conventional chemotherapy. In our patient no metastatic disease was found however she denied receiving any treatment and was subsequently lost to follow-up.

This highly aggressive signet ring cell carcinoma of gallbladder is being reported because of its rarity, its unique histomorphological features and diagnostic inadequacy of the routinely performed ultrasonography as well as highlighting the use of special stains and immunohistochemistry to exclude other possibilities. This case highlights that routine histopathological examination of all the cholecystectomy specimens is a must to facilitate the early diagnosis of aggressive signet ring cell carcinoma gallbladder. Due to the rarity of this variant there is marked paucity of knowledge regarding its pathogenesis and clinical behavior and there is an urgent need to develop an effective chemo or biological therapy to improve prognosis and final outcome of this aggressive tumor.

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