Case Report

Primary signet-ring cell carcinoma of gallbladder resembling linitis plastica: A clinical impostor of chronic cholecystitis

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ABSTRACT

Primary signet-ring cell carcinoma (SRCC) is an extremely rare and aggressive type of malignant gallbladder (GB) neoplasm, which is comprised predominantly (>50%) of signet-ring cells. Owing to its diffusely invading nature, SRCC often confers a "linitis plastica" like appearance to GB. Such a gross morphology in the background of nonspecific clinical presentation creates confusion with several other benign and more common pathological entities. This dilemma can effectively be settled through clinical, radiological, and pathological correlation. We, here, describe a case of SRCC affecting the GB in a 43-year-old lady. The tumor produced diffuse thickening of GB wall and infiltrated up to subserosa, but not beyond the GB parenchyma.

Key words: Chronic cholecystitis, gallbladder, linitis plastica, signet-ring cell carcinoma

INTRODUCTION

Gallbladder (GB) accounts for the fifth highest number of malignant gastrointestinal tumors and is the most frequent site for biliary tract carcinoma.[1] Conventional adenocarcinoma is the most common histological variant representing about 82% of all GB malignancies. Other less common malignant subtypes include papillary adenocarcinoma (6%), mucinous adenocarcinoma (5%), and adenosquamous carcinoma (4%). Squamous cell carcinoma, signet-ring cell carcinoma (SRCC), and small cell carcinoma are the secluded examples of its kind.[2] The prevalence of SRCC has been derived as 3% of all GB cancers.[3] It usually presents with pain, anorexia, weight loss and/or jaundice in elderly females. Gallstone bears its greatest risk-association.[4] Grossly, SRCC often imparts a diffusely thickened GB wall, pertinent to the "linitis plastica" appearance of the stomach. Differential considerations to such GB morphology include cholecystitis from various causes, adenomyomatosis, and multiple diverse hepatic, or systemic diseases.[5] Moreover, microscopically signet-ring cells in SRCC can be confused with inflammatory infiltrates, epithelial degeneration, signet-ring cell dysplasia, adenocarcinoma with focal signet-ring cells, mucinous adenocarcinoma, or secondary deposits.[6] Altogether its rarity, nonspecific clinical presentation, plus the multitude of macroscopic, and microscopic differentials render primary SRCC an enigmatic disease in GB.

We, hereby, describe a rare case of primary SRCC, diffusely infiltrating the entire GB wall, in a 43-year-old female who underwent total cholecystectomy after being clinically diagnosed with chronic calculous cholecystitis.

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Access this article online

Quick Response Code:

Website: www.ccij-online.org

DOI: 10.4103/2278-0513.162243

Cite this article as: Mondal K, Mandal R. Primary signet-ring cell carcinoma of gallbladder resembling linitis plastica: A clinical impostor of chronic cholecystitis. Clin Cancer Investig J 2015;4:674-7.

CASE REPORT

A 43-year-old woman was ultrasonically diagnosed with chronic calculous cholecystitis, as she initially complained about recurrent right hypochondriac pain. No other radiologically discernible organic pathology was evident at her presentation. Subsequently, she underwent laparoscopic cholecystectomy, and the specimen was subjected to routine histopathological examination.

Macroscopically, the GB was normal in size, but slightly distended in shape with its exterior being smooth and homogeneous, grayish-tan in color. Cut section revealed multiple calculi within its lumen. The GB wall was firm, solid, diffusely thickened maximally up to 0.8 cm, and its resected-surface appeared grayish-white. However, no localized mass or growth was obvious. The GB mucosa was flattened, partially ulcerated, and partially sheathed by membranous necro-hemorrhagic exudate [Figure 1]. This kind of gross GB morphology simulated cholecystitis resulting from chronic, acute-on-chronic, or xanthogranulomatous etiology; adenomyomatosis; portal hypertension; congestive cardiac failure, etc. Needless to mention that the possibility of "linitis plastica" like diffuse adenocarcinoma was only a remote consideration. Her scrutinizing clinical history and examination negated any systemic conditions; while the discrimination between local etiologies rested upon histopathological confirmation.

Microscopically, the GB mucosa was mostly ulcerated. Neoplastic cells, originating from the base of denuded mucosa, singly infiltrated GB wall transmurally up to subserosal connective tissue. These cells were almost exclusively signet-ring cells, containing abundant clear mucin-filled cytoplasm with their single hyperchromatic nuclei pushed against the cell membrane attaining a crescentic shape. Nuclear pleomorphism or mitotic figures were conspicuous, but never exuberant [Figure 2]. The residual uninvolved GB epithelia featured prominent goblet cell metaplasia, with the neoplastic cells interdigitating through muscularis propria underneath. Extracellular mucin pools were present though, constituted only a minor portion of the tumor. Considering the overall architectural pattern and cytomorphology of neoplastic cells a diagnosis of "primary SRCC in GB" was conferred. The resection margin exhibited tumoral deposits, whereas lymphovascular or perineural invasion was absent. The cystic duct lymph node was reactively hypertrophied. Her relevant physical examination, colonoscopy, plus thoraco-abdominal computed tomography failed to point out any other organic lesion.

Next up the patient underwent radical cholecystectomy with the removal of the subxiphoid port, GB fossa, and the cystic stump: None of which harbored any tumoral deposits except the proximal edge of the stump. All four lymph nodes from coeliac, paraduodenal, and paracholedochal groups were devoid of any metastatic involvement. In conformity with all findings, the tumor was staged as T2N0M0. Postoperatively she was promptly instituted upon adjuvant chemotherapy and experienced a recurrence-free follow-up for next 5 months.

DISCUSSION

Adenocarcinoma is the most common histopathological variant of GB malignancy. Irrespective of its histotype, GB carcinoma generally carries a poor prognosis. Most of the times, tumor dissemination is already present at the time of initial diagnosis. Surgery is an unlikely curative option.[4] SRCC in GB is an aggressive prototype of mucinous adenocarcinoma and is prognostically much

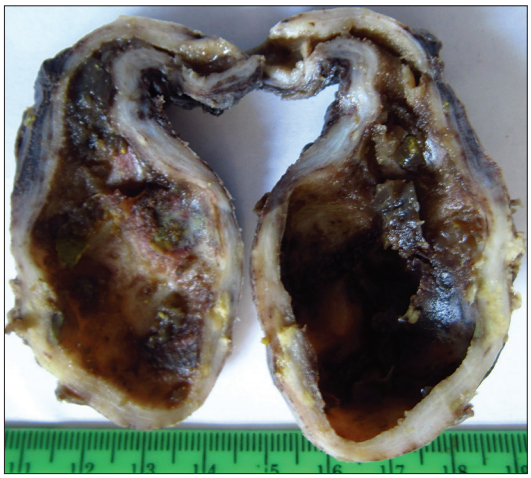

Figure 1: Primary signet-ring cell carcinoma of gallbladder: Grossly diffuse wall thickening identical to "linitis plastica" appearance, with heterogeneous grayish-white cut surface and its interior variably ulcerated, as well as covered with necro-hemorrhagic exudate

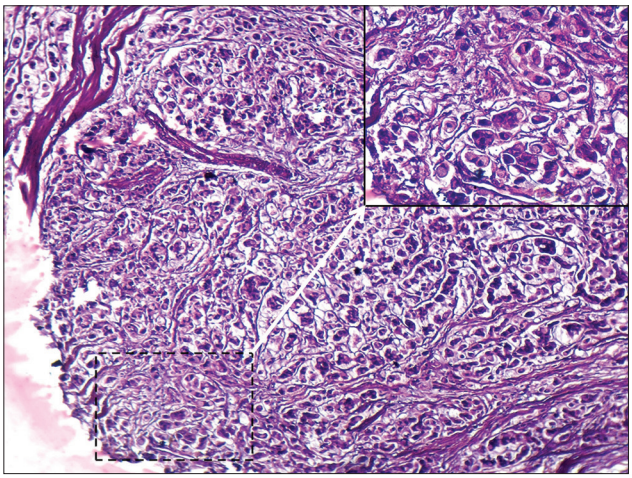

Figure 2: Primary signet-ring cell carcinoma of gallbladder: Microscopically, neoplastic signet-ring cells emanating from ulcerated surface, singly invading the gallbladder wall (H and E, ×100); containing eccentrically located hyperchromatic irregular nuclei and abundant clear mucin-filled cytoplasm (inset) (H and E, ×400)

worse than conventional adenocarcinoma. It recapitulates a growth pattern identical to the same from stomach, colon, or breast.[7] In this respect, Karagulle *et al*. described one rare tumor of stage T1N0M0 SRCC, which postoperatively rejuvenated with cutaneous dissemination after a prolonged gap of 33 months.[8] In conformity with this presentation, the discussed neoplasm was also limited to GB corresponding to stage T2N0M0, and the patient did not suffer from any metastatic disease during next 5 months.

GB SRCC grows focally, or diffusely with asymmetric/uniform wall thickening.[5] Grossly, the latter pattern is often likened to a "linitis plastica" growth pattern, produced by singly infiltrating tumor cells between tissue planes, similar to diffuse gastric adenocarcinoma.[6] However, such a GB appearance commonly prevails in acute/chronic cholecystitis, adenomyomatosis, acute hepatitis, portal hypertension, and congestive cardiac failure.[5] In this context, Ahmad and Qureshi were deceived by a diffusely thickened GB resembling "linitis plastica," which clinico-radiologically and even grossly simulated chronic cholecystitis. Finally, well-stained histopathological sections revealed the actual diagnosis of primary SRCC.[9] Accordingly, the current patient too was primordially diagnosed as chronic cholecystitis. However, immaculate histopathological examination of her GB obsoleted all those clinical impostors and subsequently yielded the definitive diagnosis of SRCC.

Microscopically, a number of neoplastic and nonneoplastic conditions may erroneously be interpreted as primary SRCC in GB. Foamy histiocytes in xanthogranulomatous or other forms of cholecystitis, degenerated epithelial cells, signet-ring cell pattern of high-grade dysplasia, focal signet-ring cell metaplasia in an otherwise diffuse adenocarcinoma, mucinous adenocarcinoma with floating signet-ring cells, and metastatic SRCC from other gastrointestinal organs are frequent sources of such misappropriation.[6] The absence of significant nuclear atypia or hyperchromasia; a heterogeneous admixture of inflammatory cells; and their confinement to mucosa potentiate the nonneoplastic histogenesis of signet-ring cells under benign conditions.[10] In addition, the predominant presence of diffusely invading signet-ring cells, lack of extracellular mucin pools, and simultaneous absence of any other organic involvement are confirmatory of primary GB SRCC.[6] Likewise, in the present case also, all those mimickers were stepwise excluded; through explicit corroboration of clinico-radiologic and microscopic features; to isolate primary SRCC as the diagnosis of choice.

The cytoplasmic mucin in signet-ring cells stains positively with alcian blue and diastase-insensitive Periodic acid-Schiff. Electron microscopy may also aid in proper identification of signet-ring cells. Imunohistochemically (IHC), GB SRCCs are CK7+, CK20−. Such a signature IHC property is useful to discriminate it from metastatic gastric and mammary SRCCs; which are both CK7+, CK20+; and CK7−, CK20−, respectively.[7] Whatsoever, Karabulut *et al*.[4] and Karagulle *et al*.[8] diagnosed their respective cases relying solely upon the characteristic histomorphology, and justified for authentic utilization of IHC or special stains in difficult cases only, particularly those with multiorganic infestation or focal signet-ring cell metaplasia in an otherwise diffuse adenocarcinoma. In the discussed case, atypical signet-ring cells were the near-exclusive neoplastic component, which involved all layers of GB wall, splitting through the muscularis proper, up to subserosal connective tissue. Such a signature histomorphology in the background of inconclusive clinico-radiological metastatic workup eventually confirmed the diagnosis of primary SRCC in GB.

CONCLUSION

With the advent of modern diagnostic methodology, primary GB malignancy is seldom encountered on routine cholecystectomy specimens from clinically suspected benign diseases. Because of its nonexpansile diffuse growth pattern, SRCC may be an incidental diagnosis in such elective cholecystectomies. Clinico-radiological correlation and detailed histopathological examination confidently differentiate primary SRCCs from its mimickers. However, in difficult situations, such discrimination may require mucin stains, IHC, or even ultrastructural investigation. By definition, SRCC is a high-grade neoplasm, whereas circumscribed lesions behave more indolently than their disseminated counterparts. However, with only handful of literatures describing this prognostically-favorable form of SRCC, more dimensions are yet to be unfolded in this field for better patient care.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Misra S, Chaturvedi A, Misra NC, Sharma ID. Carcinoma of the gallbladder. Lancet Oncol 2003;4:167-76.
2. Goldberg RM. Gallbladder cancer. In: Casciato DA, Lowitz BB, editors. Gastrointestinal Tumors. 4th ed. Philadelphia: Lippincott Williams and Wilkins; 2000. p. 210-4.
3. Albores-Saavedra J, Molberg K, Henson DE. Unusual malignant epithelial tumors of the gallbladder. Semin Diagn Pathol 1996;13:326-38.
4. Karabulut Z, Yildirim Y, Abaci I, Ilgici D, Ozyilkan O. Signet-ring cell carcinoma of the gallbladder: A case report. Adv Ther 2008;25:520-3.
5. van Breda Vriesman AC, Engelbrecht MR, Smithuis RH,

Puylaert JB. Diffuse gallbladder wall thickening: Differential diagnosis. AJR Am J Roentgenol 2007;188:495-501.
6. Adsay NV, Klimstra DS. Benign and malignant tumors of the gallbladder and extrahepatic biliary tract. In: Odze RD, Goldblum JR, editors. Surgical Pathology of the GI Tract, Liver, Biliary Tract, and Pancreas. 2nd ed. Philadelphia: Saunders Elsevier; 2009. p. 845-75.
7. Bazan F, Sanchez J, Aguilar G, Radosevic A, Busto M, Zuccarino F, *et al*. Metastatic gallbladder adenocarcinoma with signet-ring cells: A case report. J Med Case Rep 2011;5:458.
8. Karagulle E, Turk E, Kiyici H, Karadeli E, Moray G. Signet ring cell carcinoma of the gallbladder with skin metastasis: A case report. Turk Patoloji Derg 2010;26:162-4.
9. Ahmad Z, Qureshi A. Primary signet ring cell carcinoma of gall bladder: Report of an extremely rare histological type of primary gall bladder carcinoma. Br Med J Case Rep 2010;10:1136-9.
10. Ragazzi M, Carbonara C, Rosai J. Nonneoplastic signet-ring cells in the gallbladder and uterine cervix. A potential source of overdiagnosis. Hum Pathol 2009;40:326-31.