A CASE OF SIGNET-RING CELL CARCINOMA OF THE GALLBLADDER: IMMUNOHISTOCHEMISTRY AND DIFFERENTIAL DIAGNOSIS

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SUMMARY – The morphological spectrum of gallbladder carcinoma is broad and variable. Most of these tumors are tubular adenocarcinomas. There are some tumors with unusual morphology that may be difficult to classify due to their rarity. One of such tumors is the signet-ring cell carcinoma, which is a highly aggressive, mucin producing variant of gallbladder adenocarcinoma predominantly or exclusively composed of signet-ring cells. Histologically, these tumors are similar to their counterparts in other organs such as stomach, colon and breast, and should not be misinterpreted as metastatic carcinoma from one of these primary sites. The literature about this variant of carcinoma is sparse and little is known about it. We found only three cases of signet-ring cell carcinoma of the gallbladder previously reported. We present the case of an 86-year-old woman with signet-ring cell carcinoma of the gallbladder and discuss the potential diagnostic dilemmas and pitfalls.

Key words: *Carcinoma signet ring cell; Gallbladder neoplasms – diagnosis; Gallbladder neoplasms – pathology; Case report*

Introduction

The morphological spectrum of gallbladder carcinoma is broad and variable. Most of these tumors are tubular adenocarcinomas. There are some tumors with unusual morphology that may be difficult to classify due to their rarity[1]. One of such tumors is the signet-ring cell carcinoma (SRCC), which is a highly aggressive, mucin producing variant of gallbladder adenocarcinoma predominantly or exclusively composed of signet-ring cells[2-4]. Histologically, these tumors are similar to their counterparts in other organs such as stomach, colon and breast, and should not be misinterpreted as metastatic carcinoma from one of these primary sites[5-7].

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To our knowledge, only two cases of gallbladder SRCC have been reported in English literature[2,3] and one case in Japanese[4] literature, and little is known about this histological variant.

Herein we present a case of gallbladder SRCC in an 86-year-old female.

Case Report

An 86-year-old female with diagnosed hypertension, Parkinson syndrome and bilateral coxarthrosis presented with a sudden onset of icterus and a history of intermittent abdominal pain over the course of one year. Laboratory tests showed anemia and elevated bilirubin, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, amylase, urea and creatinine. She was admitted to the hospital for suspicion of acute biliary pancreatitis.

Abdominal ultrasonography revealed a normal sized gallbladder with a gallstone, as well as multiple liver

nodules measuring up to 2 cm in diameter. Ductus choledochus was dilated and measured up to 1 cm in diameter. Contrast-enhanced endoscopy was not performed because the patient had a medical history of allergic reactions. Instead, explorative laparotomy was suggested.

Laparotomy revealed a normal sized gallbladder with thickened wall and fibrous serous adhesions. On the surface of the liver there were multiple metastases measuring up to 2 cm in greatest diameter. Some enlarged regional lymph nodes were also present. Cholecystectomy was performed and gallbladder was referred for histopathologic examination.

Grossly, the gallbladder measured 8.5x4.5 cm. On the cut surface, there was a marked whitish mural thickening measuring up to 3 cm in diameter. There were collections of bile in the lumen and a yellowish gallstone measuring up to 2 cm in diameter. The cystic duct was dilated and partially occluded with a white to yellowish tumor.

Microscopic examination showed an infiltrating carcinoma with individual signet-ring cells comprising more than 90% of the tumor (Fig. 1A). The cells had abundant intracellular mucin and were seen in small clusters and diffuse sheets (Fig. 1B). No areas of conventional adenocarcinoma were seen. Tumor cells were present in all layers of the gallbladder wall. They were alcian-PAS positive and diastase resistant (Fig. 1C). There was lymphatic and vascular, as well as

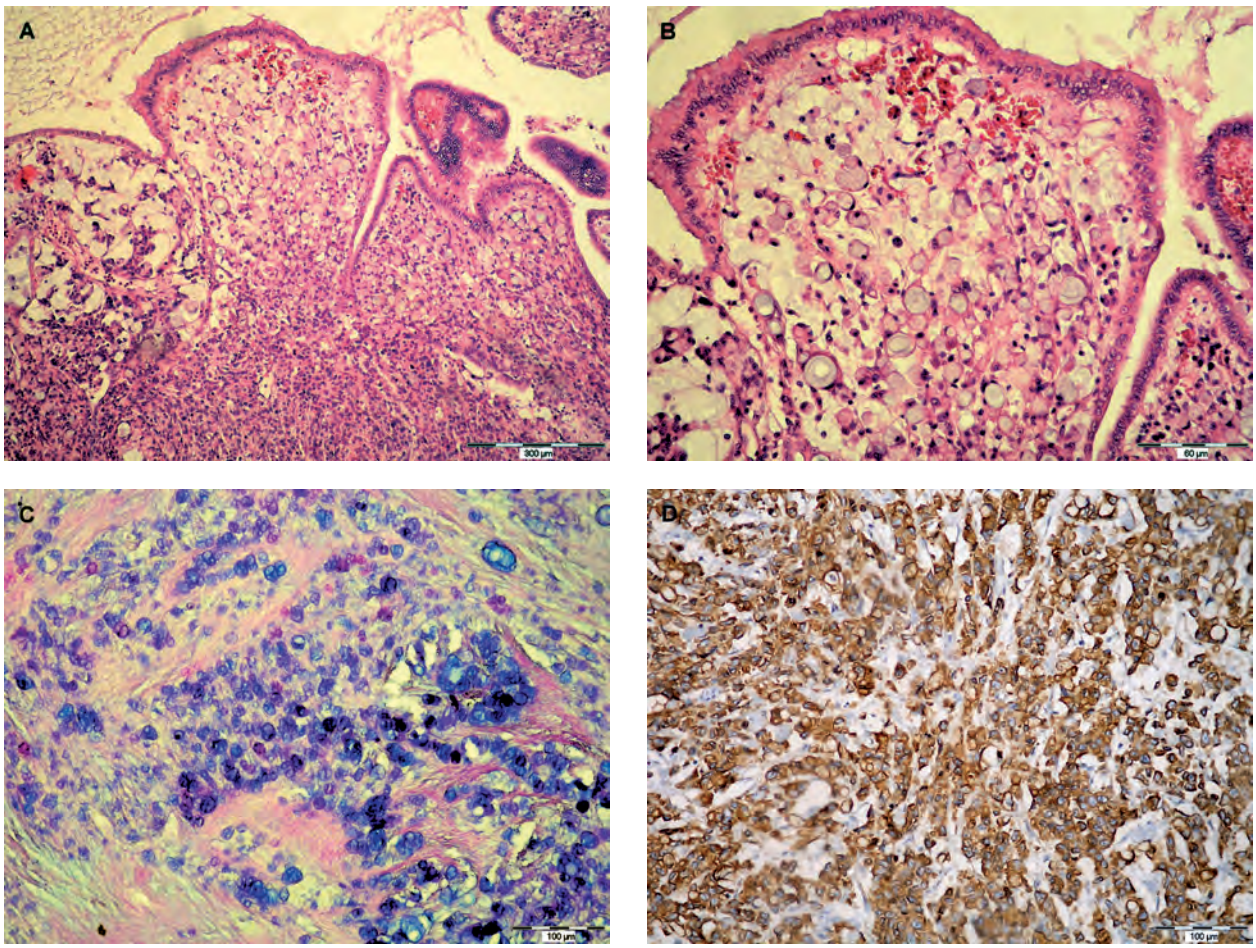

Fig. 1. (A) Microscopic examination showed an infiltrating carcinoma with individual signet-ring cells comprising more than 90% of the tumor (HE stain, scale bar is 300 μm); (B) the cells had abundant intracellular mucin and were seen in small clusters and diffuse sheets (HE stain, scale bar is 60 μm); (C) tumor cells were alcian-PAS positive and diastase resistant (alcian – PAS stain, scale bar is 100 μm); and (D) immunohistochemically, tumor cells were positive for cytokeratin AE1/AE3 (cytokeratin AE1/AE3 stain, scale bar is 100 μm).

perineural invasion. Immunohistochemically, tumor cells were positive for cytokeratin (CK) AE1/AE3 (Fig. 1D), CK7, CK8, CK18, CK20, carcinoembryonic antigen, epithelial membrane antigen, p53 and MUC1. Cytokeratin 5/6, MUC-2, neuron specific enolase, chromogranin A, synaptophysin, progesterone and estrogen were negative.

The diagnosis of SRCC of the gallbladder was established. On postoperative day 4, the patient died. The exact cause of death was not established because autopsy was not performed.

Discussion

To our knowledge, we report the fourth case of SRCC of the gallbladder. Krunic *et al.*[2] have reported one case of disseminated gallbladder SRCC in a 38-year-old man who received radiotherapy and chemotherapy. The patient was alive twenty months after the original diagnosis. The second case, reported by Karabulut *et al.*[3], was a 76-year-old male patient with SRCC who died within three months of the diagnosis despite radical surgery and chemotherapy. The third case was a patient with SRCC and anomalous pancreaticobiliary ductal union. It has been reported in Japanese language by Yamauchi *et al.*[4] and we have no additional information on this case.

Signet-ring cell carcinoma can arise from virtually any organ. However, more than 90% of SRCC cases in humans arise from the stomach, breast and colon[5-7]. Because of its rarity, gallbladder SRCC may be misinterpreted as a metastatic carcinoma from the aforementioned organs.

A variety of immunohistochemical markers have been employed to distinguish SRCC from the stomach, breast and colon. A panel of immunohistochemistry markers can be used to facilitate the diagnosis of metastatic SRCC from these organs[7]. However, before performing immunohistochemical staining, obtaining a complete clinical history is the first step in the evaluation of the possible metastatic SRCC. The most frequently used markers are CK7, CK20, MUC1, MUC2 and estrogen. The majority of gastric SRCC show CK7, CK20 and MUC2 positivity but are MUC1 negative. Breast SRCC are mostly CK7, MUC1 and estrogen positive but CK20 negative, whereas colon SRCC are usually CK20 and MUC 2 positive and CK7 and MUC1 negative[5-7].

In the case presented, clinical data and growth pattern indicated a primary gallbladder carcinoma. Furthermore, the immunoprofile was consistent with conventional biliary-type adenocarcinoma. It was different from the immunoprofile of the stomach, breast and colon SRCC, thus providing additional support for its gallbladder origin[8-10].

A condition that could be misdiagnosed as gallbladder SRCC is the accumulation of non-neoplastic signet-ring cells in the gallbladder mucosa[11-13]. Four cases of benign signet-ring cell aggregates in the gallbladder mucosa associated with focal ulceration and inflammation have been described by Michal *et al.*[11], Suri *et al.*[12] and Raggazi *et al.*[13]. The underlying biological mechanism is still unclear. Suri *et al.*[12] ruled out the hypothesis of metaplastic genesis because signet-ring cells are not part of the normal adult cell population. Michal *et al.*[11] attributed the presence of signet-ring cells in the gallbladder to the combined effect of mucosal necrosis and ulceration. Ragazzi *et al.*[13] suggest that in mucin-producing mucosa, focal ischemia could cause sloughing and disaggregation of the cells, leading to signet-ring changes.

The main morphological features that allow for differentiation between non-neoplastic and neoplastic signet-ring cells are the confinement of non-neoplastic cells to the mucosal surface or glandular lumina and their lack of cellular atypia, nuclear hyperchromasia, prominent nucleoli or mitoses[14]. Furthermore, non-neoplastic signet-ring cells are usually accompanied by prominent inflammatory and necrotizing changes[14,15]. In dubious cases, immunohistochemistry could play an important role. Comparative analysis done by Wang *et al.*[14] showed that non-neoplastic signet-ring cells, in contrast to neoplastic cells, exhibit E-cadherin expression, no cell proliferation, and no p53 mutation.

In our case, clinical data, histologic findings and immunohistochemistry ruled out the possibility of metastasis and non-neoplastic signet-ring cell changes.

In conclusion, the incidence of gallbladder signet-ring cell carcinoma is very low. Therefore, it is important to rule out the possibility of metastasis from other organs such as stomach, breast and colon. Furthermore, the occurrence of benign, clinically insignificant signet-ring cell changes of gallbladder mucosa could represent a potential diagnostic pitfall, especially in biopsy specimens, which can lead to overdiagnosis and result in malpractice issues.

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Sažetak

SLUČAJ KARCINOMA STANICA PRSTENA PEČATNJAKA ŽUČNOG MJEHURA: IMUNOHISTOKEMIJA I DIFERENCIJALNA DIJAGNOSTIKA

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Morfološki spektar karcinoma žučnog mjehura širok je i raznolik. Većina tumora su tubularni adenokarcinomi. Postoje neki tumori neobične morfologije koje je teže klasificirati zbog njihove rijetkosti. Jedan od takvih tumora je karcinom stanica prstena pečatnjaka, visoko agresivna varijanta adenokarcinoma žučnjaka koja proizvodi sluz, a pretežito je ili isključivo sastavljena od stanica tipa prstena pečatnjaka. Histološki, ovi su tumori slični svojim pandanima u drugim organima kao što su želudac, debelo crijevo i dojka te ih se ne bi smjelo pogrešno interpretirati kao metastatske karcinome iz spomenutih organa. Literatura na temu ovoga tipa karcinoma je rijetka i o njemu se malo zna. Našli smo samo 3 prethodno objavljena slučaja ovoga karcinoma. U članku se prikazuje slučaj 86-godišnje žene s karcinomom stanica prstena pečatnjaka žučnjaka i raspravlja o potencijalnim dijagnostičkim dvojbama i mogućim pogreškama.

Ključne riječi: *Karcinom stanica prstena pečatnjaka; Novotvorine žučnjaka – dijagnostika; Novotvorine žučnjaka – patologija; Prikaz slučaja*