SIGNET RING CELL CARCINOMA OF THE GALLBLADDER; REPORT OF A CASE AND REVIEW OF THE LITERATURE

Safrakesesinin yüzük hücreli karsinomu; Olgu ve literatür sunumu

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ABSTRACT
Primary signet ring cell carcinoma is a rare and aggressive neoplasm of the gall bladder. Only few cases of this type have been reported till date and detailed knowledge about this entity is lacking. Signet ring cell carcinoma in a 54 year old man is reported here. He presented with non specific symptoms of upper abdominal pain and anorexia. Ultrasonography revealed a polypoid mass in the body of gall bladder. The diagnosis can be confused with non-neoplastic benign signet ring cells. However the benign signet ring cells do not encompass full thickness of the wall and are associated with inflammatory cells. An early diagnosis with the help of imaging study and special stains on the biopsy specimen like periodic acid Schiff and immunohistochemistry can help in patient survival. Radical surgery was done and chemotherapy given. Presently the patient is under follow up without obvious metastasis.

Key words: Gallbladder, signet ring cell carcinoma, immunohistochemistry.

INTRODUCTION
Gallbladder carcinoma is the commonest malignant tumour of biliary tract with higher incidence in females and increasing age (1,2). Most of the gall bladder cancers are adenocarcinomas. Presence of gall stones is an independent risk factor for any gall bladder cancer and is mostly of cholesterol type (2).

Signet ring carcinoma (SRCC) of gall bladder is a rare tumor accounting for about 3% of all gall bladder carcinomas (3). It is an aggressive variant of mucinous adenocarcinoma and has worse prognosis (4,5). The tumors show a growth pattern similar to gastric, colon and breast signet ring cell carcinomas and may be mistaken as metastatic carcinoma. Though SRCCs are found more in elderly people, younger people may also be affected (6).

Other carcinomas include adenosquamous carcinomas, squamous cell carcinomas, small cell carcinoma. Rare malignancies include carcinosarcoma, malignant melanoma, non Hodgkin lymphoma.

CASE
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A 54 year old lady presented with right upper abdominal pain, anorexia and nausea. On ultrasonographic examination cholelithiasis with chronic cholecystitis was detected (Figure 1A). Routine hematological examinations were within normal limits except mild anemia. Raised alkaline phosphatase was noted in biochemical tests. The patient underwent laparoscopic cholecystectomy and the gall bladder was sent for histopathological examination.

The gall bladder measured 6x3.5 cms The wall was thickened and the lumen showed a polypoid mass measuring 0.5x0.3 cms (Figure 1B). The mucosa of the adjoining area was bile stained. One celiac lymph node was noted. Microscopic examination showed a tumor comprising signet ring cells diffusely infiltrating all the layers of gall bladder (Figure 1C,1D). The tumor arose from the subepithelial layer of mucosa. Mitosis and nuclear atypia were present. No definite lymphovascular emboli or perineural invasion could be detected. The tumor did not extend beyond gall bladder and the celiac lymph node showed reactive hyperplasia-stage pT2NoMx. Periodic Acid Schiff (PAS) stain (Figure 2A) demonstrated the intracellular as well as extracellular mucin (in less than 10% of tumor). Immunohistoc hemistry (IHC) with cytokeratin 7 (CK7) showed positivity (Figure 2B) in the tumor cells while cyto keratin 20 (CK20) was negative.

The patient then underwent metastatic work-up and followed by completion of extended cholecystectomy via laparotomy route. The histopathological examination of liver tissue and lymph nodes did not show any evidence of remnant malignancy.

The patient received post operative chemotherapy with 5-Flurouracil (5FU) infusion for 3 months. Presently, he is under follow up without any evidence of recurrence.

**DISCUSSION**

Gallbladder cancer is common and it is the fifth most common malignant neoplasm of gastrointestinal tract and about 90% of these are adenocarcinomas (1). The SRCC subtype is a rare and form of mucinous adenocarcinoma which frequently metastasises to regional lymph nodes, peritoneal surfaces and lung (5,6). SRCC commonly arises from the stomach, colon and breast. Hence it is important to rule out metastasis from these sites before diagnosing a gall bladder SRCC.

Initial detection of gall bladder carcinoma as a polypoid lesion occurs in 15-20% of cases (7,8). However SRCC may present only as diffuse thickening of the wall as noted by Ahmad Z et al (9). Histologically it is characterized by the presence of rounded cells with clear and or mucinous cytoplasm with hyperchromatic peripheral nucleus. Extracellu-
lar mucin may be present. The tumors are PAS positive diastase resistant. The usual IHC pattern of gall bladder SRCC is CK7 positive, CK20 and estrogen receptor (ER) negative. Gastric SRCC are CK7 and CK20 positive, colonic SRCC are CK7 and CK 20 negative while breast SRCC are mostly CK7 and CK20 negative and ER positive. Our case was PAS (with diastase) positive and with IHC was CK7 positive, CK 20 and ER negative. This is consistent with findings of other workers like Bazan F et al (4) and Panić I et al (5).

Figure 2: A) Signet ring cells with intracellular mucin, PAS stain, x400, B) Signet ring cells showing CK7 positivity, IHC stain X 400.

Non neoplastic signet ring cells can be easily confused with SRCC. These cells show positivity for cytokeratin by IHC and also for mucicarmine as noted by Ragazzi M et al (10). According to them lack of nuclear atypicality, arrangement in superficial and intraluminal nests, and the admixture of histiocytes and other inflammatory cells indicate the benign nature of these cells. On the other hand p53 mutation by IHC and electron microscopy can help to establish the true identity of SRCC in difficult cases (4,6). SRCC shows mucin vacuoles and intracytoplasmic lumina by electron microscopy.

This patient is doing well after 3 months of chemotherapy (5-FU). This patient is surviving without recurrence as the tumour was detected at an early stage. Even aggressive surgeries like major hepatectomies and bile duct resections fail to cure the patients of gall bladder carcinoma at an advanced stage (11).

In conclusion; the nature of the signet ring cells and also possibility of metastasis needs to be determined by clinico-radiological correlation and special tests like IHC and electron microscopy (when in confusion). Over aggressive surgeries must be avoided. SRCC of gall bladder worsens the patient’s prognosis and with only a few literatures available, emphasis for more research in this field is vital for better patient care.

REFERENCES
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