Case Report

Mixed adenoneuroendocrine carcinoma in gallbladder with ovarian metastasis of adenocarcinoma component: A case report

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ABSTRACT

Mixed adenoneuroendocrine carcinoma (MANEC) are uncommon tumors exhibiting both adenocarcinomatous and neuroendocrine differentiation with both components constituting at least 30% of the total cellular population. We report a case of a 39-year-old lady, presenting as a case of Krukenberg's tumor, and the primary was found to be in the gallbladder which on pathological examination revealed a MANEC.

Key words: Gall bladder, Krukenberg's tumor, Mixed adenoneuroendocrine carcinoma

Adenocarcinoma is the most common histologic subtype of gallbladder malignant tumors while neuroendocrine tumors (NET) account for a mere 0.5% [1]. Mixed adenoneuroendocrine carcinomas (MANEC) of the gallbladder are even rarer. Our case of MANEC presenting as Krukenberg's tumor falls into the rarest of the rare category. The first description of a mixed tumor with neuroendocrine (NE) and exocrine components in the gastrointestinal tract was published by Cordier in 1924 [2]. The terminology "mixed adenoneuroendocrine carcinomas" (MANEC) for these mixed tumors of the gastrointestinal tract was standardized in 2010 by the World Health Organization (WHO), with each component comprising at least 30% of the tumor volume [3]. WHO subsequently incorporated MANEC into the broader category of mixed NE non-NE neoplasm, where the 30% threshold for each component was maintained, with the term "adeno" substituted with "non-neuroendocrine" to incorporate other histotypes.

CASE REPORT

A 39-year-old lady presented to the surgical oncology outpatient department (OPD) in September 2024 with a history of pain and abdominal distension of one and a half months duration with no signs of obstructive jaundice.

The patient was afebrile and her vitals were within normal limits. Her CA-125 was 203 U/mL, carcinoembryonic antigen (CEA): 7.2 ng/mL, alpha-fetoprotein: 0.1 ng/mL, lactate dehydrogenase: 370 U/L, beta-Hcg: 0.4 m UI/mL.

Pre-operative magnetic resonance imaging and positron emission tomography-computed tomography scan revealed lobulated cystic mass lesions in the pelvic cavity with the left mass measuring 13 × 10 × 12 cm and the right mass measuring 6 × 4 × 7 cm, multiple bilaterally enlarged pelvic lymph nodes and distended gall bladder measuring 29 × 18 × 19 mm with mucosal thickening.

She was initially suspected as a case of carcinoma ovary and underwent debulking surgery. Intraoperatively, bilateral adnexal masses, bilateral pelvic lymph nodes, and omentum were removed with retroperitoneal tissue sampling. Intraoperative, the gallbladder was found to be distended, pyocele-like, and radical cholecystectomy was performed with a 1–2 cm liver wedge removed. Ovarian masses and gallbladder were sent for a frozen section.

On gross-section, both ovaries were enlarged with bosselated outer surface, intact capsule, and grey-white solid cut surface with few cystic areas. The gallbladder wall was thickened with the posterior wall being adherent to the liver bed. The frozen section revealed foci of high-grade adenocarcinoma with a possibility of Krukenberg's tumor in the ovaries and a malignant tumor of the gallbladder. The post-operative period was uneventful. The patient was discharged on the 12th post-operative day.

Histologically, the gallbladder showed a mixed tumor comprising of high-grade NE component and high-grade adenocarcinoma, both accounting for more than 30% each

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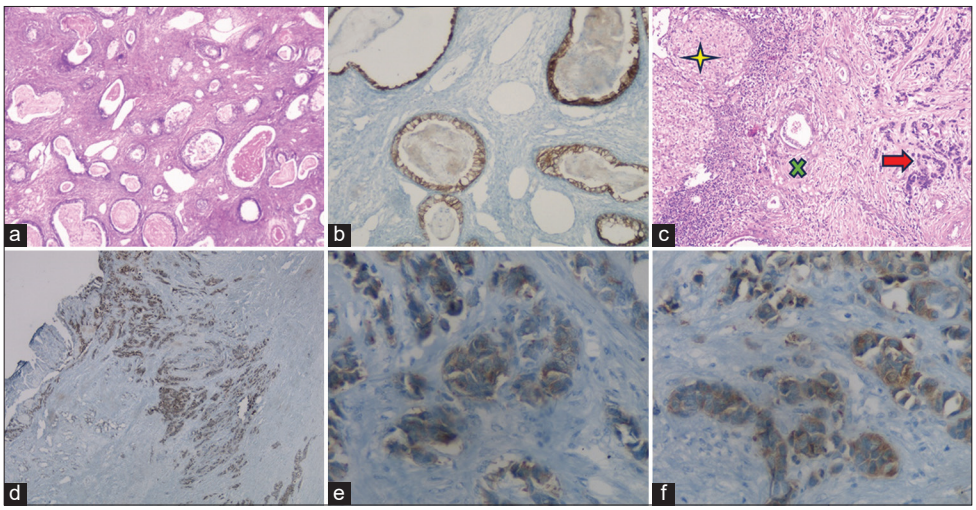

Figure1: (a) Adenocarcinoma metastatic deposits in ovary (H and E, x100). (b) CK7 positive staining in adenocarcinoma deposits in ovary (immunohistochemistry, x200). (c) Gall bladder showing both adenocarcinoma and neuroendocrine tumor and wedge liver resection (Haematoxylin and Eosin, x100). (d) CD56 positive neuroendocrine carcinoma in gallbladder (immunohistochemistry, x200). (e) Synaptophysin positive neuroendocrine carcinoma in gallbladder (immunohistochemistry, x400). (f) Chromogranin positive neuroendocrine carcinoma in gallbladder (immunohistochemistry, x200)

of the total tumor population. Both ovaries revealed multiple foci of adenocarcinoma with necrotic debris in the lumen of adenocarcinoma glands. Two out of four lymph nodes in periportal tissue showed metastatic adenocarcinoma with extranodal extension. One out of two lymph nodes in pericholedochal tissue showed metastatic deposits of adenocarcinoma without extranodal extension.

On immunohistochemistry CK7, CK19, CA19.9, and CEA were positive in the glandular component of both ovarian and gall bladder mass, and chromogranin, synaptophysin, and CD56 were positive in the solid NE part of the gallbladder (Fig. 1a-f). The proliferation index was 70% in the highest proliferative area. Ovarian mass was negative for PAX-8 and CA-125. The tumor was diagnosed as MANEC of the gall bladder with local invasion into the liver and metastasis of adenocarcinoma component to bilateral ovaries (Krukenberg's tumor).

DISCUSSION

Adenocarcinomas comprise almost 90% of malignant tumors in the gall bladder and NETs account for <0.5%. MANEC of gallbladder are extremely rare tumors. MANEC of the gallbladder is an extremely rare tumor with most patients presenting with non-carcinoid complaints like pain abdomen or discomfort or cholelithiasis-like symptoms, indicating carcinoid-causing chemicals may not be produced or may be sequestered in the biliary tree.

In 2000, the WHO classification of endocrine tumors, mixed exocrine endocrine tumors was defined as neoplasms in which each component formed at least 30% of the tumor. In 2010, the WHO classification these were designated as MANECs. In these tumors, both components are malignant. In our case, both exocrine and endocrine components were present equally in the tumor. Hence, the tumor qualified as a mixed tumor.

The normal biliary tree contains focally distributed few enterochromaffin cells in the gallbladder, large bile ducts, and hepatic hilum [4]. Therefore, the histogenesis of biliary MANECs is debated.

Some believe that MANECs follow a sequence of metaplasia-dysplasia-carcinoma, originating either from intestinal/gastric metaplasia (which contains NE cells) or from dysplastic biliary epithelium [5]. Supporting this view, an association between chronic inflammation, intestinal metaplasia (IM), and gallbladder cancer has been well established [6]. Differentiation/maintenance of intestinal epithelium depends on *CDX2* gene expression, as has been demonstrated in the normal digestive tract and in gallbladders with IM [7]. A recently reported case of gallbladder MANEC with extensive IM and focal high-grade dysplasia showed intense CDX2 positivity on the NET [8]. Moreover, in a series of 274 malignant biliary neoplasms, NE cells detected by immunohistochemistry were present in 22–29% of biliary carcinomas (depending on the location) [9]. Curiously, NE cells were only observed in hilar cholangiocarcinomas with chronic cholelithiasis, being consistently absent from tumors without chronic inflammation [9]. All of this evidence supports that at least some biliary MANECs may follow a metaplasia-dysplasia-carcinoma or a dysplasia-carcinoma sequence. Others have suggested that MANECs could originate from cancer stem cells. In fact, a series of 90 gastrointestinal NETs showed that expression of cancer stem cell marker CD133 is common in digestive NETs, and especially so in MANECs (63.6%) [10].

The degree of differentiation of each component determines the prognostic outcome of these tumors. Gastrointestinal MANECs have been provisionally classified by La Rosa *et al*. as (a) high-grade malignant which contain adenoma/adenocarcinoma and poorly differentiated NE carcinoma (small, intermediate, and large cell type), (b) intermediate-grade malignant which contain mixed adenocarcinoma and G1/G2 NET. Besides these two well-defined types, a provisional category that is not included in the WHO 2010 classification has been described. This is an indolent low-grade malignant mixed tumor that has an adenomatous component and

NET and is designated as a mixed adeno NET and not as carcinoma in view of indolent behavior [11]. Lewin in 1987 classified these tumors as (a) composite or collision tumors showing exocrine and endocrine components in separate areas of the same lesion, (b) combined tumors with both components intimately mixed, and (c) amphicrine tumors when exocrine and NE features are present in the same neoplastic cell. In our case, both components were present separately in the same lesion in the gallbladder and adenocarcinoma had metastasized to bilateral ovaries [12].

The most common sites for MANEC tumors in the gastrointestinal tract are the colon, rectum, appendix, and stomach. Other sites include the esophagus, bile duct, gallbladder, pancreas, and cecum.

Surgical treatment of these tumors ranges from simple cholecystectomy to minor hepatectomy with concomitant lymph node dissection and extrahepatic bile duct resection depending on the extent of tumor invasion. No standardized chemotherapy protocol exists for these tumors with treatment depending on the degree of MANEC differentiation. Various drugs such as doxorubicin, 5-fluorouracil, cisplatin, and streptozocin have been used either alone or in combination, with poor overall response rates [13]. Biotherapy using somatostatin analogs has been assessed in the treatment of metastatic disease; it has demonstrated tumor static effects with symptomatic improvement [14].

CONCLUSION

Gall bladder MANEC is a rare malignancy with aggressive biological behavior. Preoperational pathological diagnosis and identification of clinical stage are of vital importance. Unfortunately, gallbladder MANEC is a histopathologic diagnosis, thus most of the times, it is demonstrated postoperatively and confirmed by the expression of synaptophysin and chromogranin A. complete surgical resection is the mainstay of therapeutic management. In addition, the stage of the disease and the histopathological mapping of the lesion could affect decision-making for adjuvant chemotherapy, but ultimately these two elements seem to define the prognostic course of each patient. Consequently, to evaluate the optimal diagnostic and therapeutic strategies for gall bladder MANEC, the enlargement of the available literature and the design of further trials are required. Our patient had an uneventful post-operative recovery and was scheduled to visit oncology OPD after 2 weeks for further decisions regarding chemotherapy.

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