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RAPID COMMUNICATION

A rare case of easily misdiagnosed primary mucoepidermoid carcinoma of the liver

To the editor,

Mucoepidermoid carcinoma (MEC) is a common malignancy of the salivary glands, which account for approximately 30% of all malignant salivary gland neoplasms that originate in both the major and minor glands.[1] But it is relatively rare at other organs, extremely rare in the hepatobiliary system. To the best of our knowledge, since primary MEC of the liver was first reported in 1971,[2] no more than 20 cases have been reported worldwide. The cellular morphology of MEC can be easily misdiagnosed as adenosquamous carcinoma (ASC). In view of the poor prognosis of MEC, we herein report the morphological, histochemical, immunohistochemical, gene sequencing results and ultrastructural features, which distinguished from ASC through a misdiagnosed case.

A 62-year-old Chinese male presented to local hospital due to epigastric pain with aggravation after eating for one week. He had no vomiting, diarrhea or fever, no remarkable medical or family history of malignancy. Physical examination revealed mild tenderness beneath the xiphoid process. Ultrasonography showed an intrahepatic mass in the left lateral lobe. Enhanced computed tomography (CT) scan showed the lesion measuring 6.1cm × 5.3 cm with mild marginal enhancement in arterial phase, moderate marginal enhancement in portal phase and gradually centripetal enhancement in delayed scan (Fig. 1A, Fig. S1 A–C). Laboratory tests revealed no meaningful abnormality except for elevated serum carcinoembryonic antigen (CEA) at 60.68 ng/mL (normal range, <10), carbohydrate antigen 153 (CA153) at 16.09 U/mL (normal range, <15) and CA19-9 at 1180.38 U/mL (normal range, <30). He had normal serum alpha-fetoprotein (AFP) level, negative hepatitis B viral antigen and hepatitis C antibody assays. The patient underwent an open left lateral hepatic lobectomy with hepatic hilar lymphadenectomy (Fig. 1A). Histologically, the tumor nests are similar to squamous carcinoma and adenocarcinoma cells (Fig. 1B). In pericancerous tissues, perineural and vasal invasion were noted and bile duct dysplasia was visible in the interlobular portal area (Fig. 1C). One of the nine resected lymph nodes showed tumor metastasis (Fig. 1C, Fig. S1D,E). Immunohistochemically, the tumor cells were negative for AFP, Hepatocyte, CD10, CD34, SMA and Calponin, while strongly positive for CK5/6, CK7, CK8/18, CK19 and P63, with Ki-67 up to 40% (Fig. 1D).

The patient was diagnosed with primary adenosquamous carcinoma of the liver by local hospital. Pathological consultation by our pathology department showed tumor nests admixed with epidermoid, mucinous and intermediate cells without clear boundaries (Fig. 1C–E). Histologically, focal keratinization was infrequently seen in the epidermoid cells, but no prominent keratin pearl. Mucinous cells were large volume, cuboidal or columnar shape, with pale cytoplasm, but no prominent gland formation. Immunohistochemically, CK5/6 and P63 were negative in mucinous cells (Fig. 1E). Based on these features, the patient was diagnosed as primary high-grade MEC of the liver.

Due to the epidemic of COVID-19, the patient was not reviewed routinely. Three months after surgery, he was revisited in local hospital with recurrent epigastric pain. CT scan showed a recurrent mass lesion in the left internal lobe of the liver. A whole-body positron emission tomography-computed tomography (PET/CT) validated tumor recurrence of the left hepatic internal lobe and no primary tumors of other organs was observed (Fig. 1F). After transferred to our hospital, three-dimensional visualization was performed and revealed that the portal vein and middle hepatic vein were not invaded, but the common hepatic artery (CHA), proper hepatic artery (PHA) and the initial part of the gastroduodenal artery (GDA) were wrapped around the tumor (Fig. 1G, Fig. S1 F–H). Cancer precision medicine test by next-generation sequencing showed no clinically significant targeted therapy (Fig. 1H, Fig. S2). Immunohistochemistry for PD-L1 showed tumor proportion score was 1% and combined positive score was 2,

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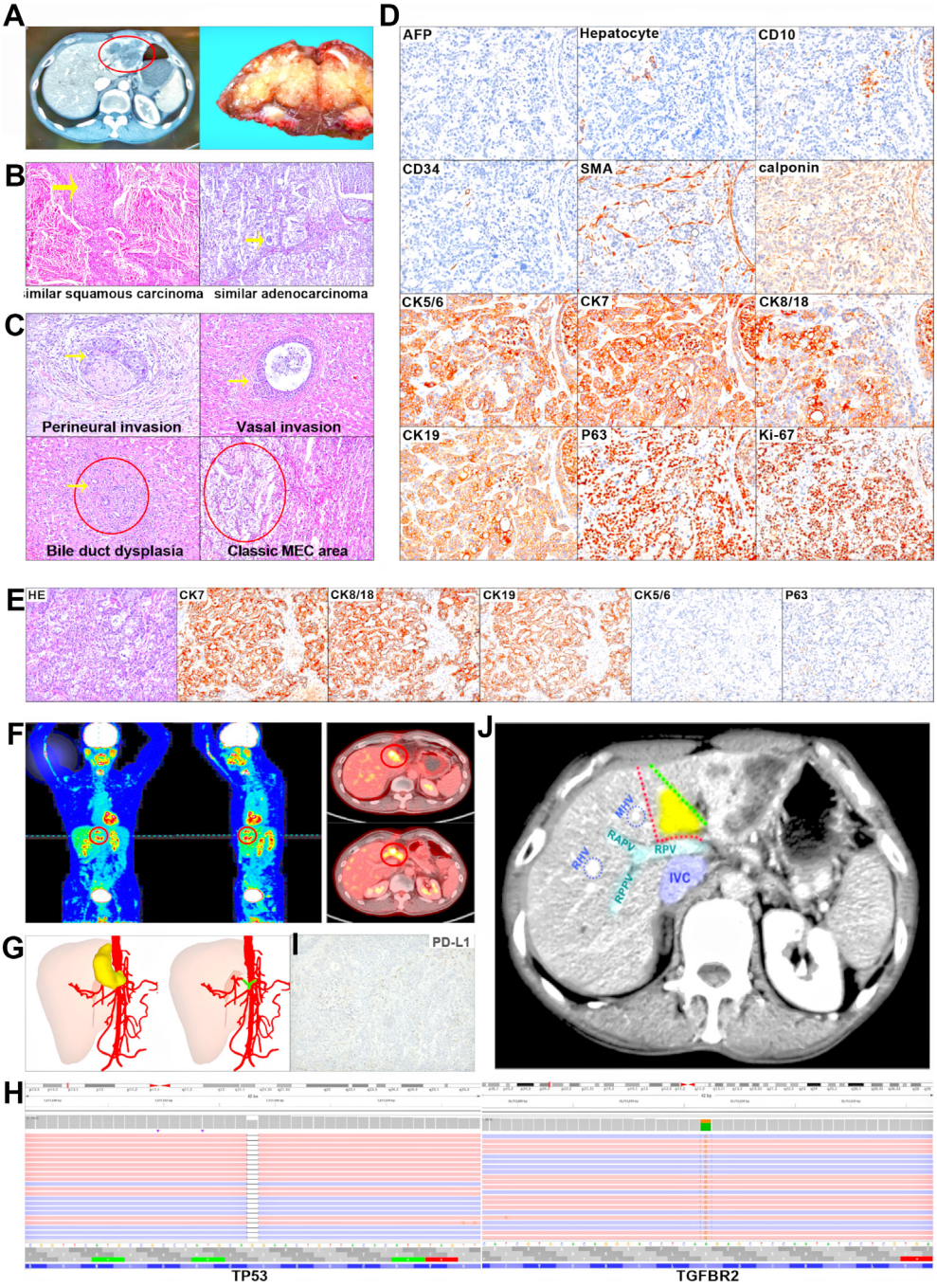

Figure 1 Characteristics of the tumor. **(A)** Imaging and morphological features of the tumor. Enhanced CT scan showed the enhancement characteristics of the tumor. Resected specimen of the left lateral lobe of the liver. **(B)** Histologically, the tumor nests are similar to squamous carcinoma and adenocarcinoma cells (HE, 200 ×). **(C)** Perineural invasion, vasal invasion and interlobular bile duct dysplasia were visible (HE, 200 ×). One resected lymph nodes showed tumor metastasis (Classic MEC area) (HE, 200 ×). **(D)** Immunohistochemical characteristics of the tumor in local hospital. The tumor cells were negative for AFP, Hepatocyte, CD10, CD34, SMA and Calponin, while strongly positive for CK5/6, CK7, CK8/18, CK19 and P63, with Ki-67 up to 40% (200 ×). **(E)** Pathological consultation by our pathology department. The tumor nests admixed with epidermoid, mucinous and intermediate cells without clear boundaries (HE, 200 ×). Immunohistochemically, mucinous cells were strongly positive for CK7, CK8/18 and CK19, but negative for CK5/6 and P63 (200 ×). **(F—H)** Evaluation of tumor recurrence. **(F)** PET/CT validated tumor recurrence of the left hepatic internal lobe. **(G)** 3D visualization located the site of tumor recurrence. CHA, PHA and the initial part of GDA were wrapped around the tumor. **(H)** TP53 and TGFBR2 sequencing results. **(I)** Immunohistochemically, tumor cells were negative for PD-L1 (200 ×). **(J)** Reconsideration of primary surgical planning.

predicting the poor efficacy of immunotherapy (Fig. 1I). Considering the impossibility of radical R0 resection, the patient received chemotherapy with gemcitabine and oxaliplatin (GEMOX regimen). After three rounds of chemotherapy, the efficacy was evaluated as stable. Unfortunately, he had to stop chemotherapy because of intolerable side effects and died 10 months after surgery.

The etiology and pathogenesis of hepatic MEC remains unclear. On the current speculations, hepatic MEC may arise from a congenital cyst or the terminal bile duct in association with squamous metaplasia. Patients with liver MEC had extremely poor prognosis with a median survival of 4 months.[3] Only one patient who received oral administration of S-1 combined with local radiotherapy after surgery has achieved a long-term survival of more than 10 years.[4] What is more worthy of reflection from our case was that the patient received left lateral lobe resection for the first time (Fig. 1J green line), but the recurrent lesion was located at the margin of the left internal lobe (Fig. 1J yellow region). We speculated that anatomical left hemihepatectomy (Fig. 1J red line) might be meaningful in prolonging his disease-free survival. The sequencing results also failed to find clinically meaningful targeted treatments.

Primary MEC in the hepatobiliary system is extremely rare, and the leading site of MEC is located in the salivary glands. Therefore, its degree of malignancy mainly refers to the classification of salivary gland tumors. According to 2017 WHO classification of head and neck tumors, MEC can be divided into low differentiated, moderately differentiated, and high differentiated.[1] In this case, liver MEC is mainly low differentiated, which explains the rapid progress of the patient's condition. Besides, MEC can be classified as a particular type of biliary carcinoma in primary liver tumors. It can refer to intrahepatic cholangiocarcinoma for clinical staging.[5] The tumor had vascular invasion and regional lymph node metastasis in this case, but no distant metastasis was seen. Its clinical stage was T2N1M0.

MEC is composed of epidermoid, intermediate, and mucinous cells. Low differentiated MEC, mainly consisting of epidermoid cells and intermediate cells, is challenging to distinguish from ASC. However, ASC has squamous cell carcinoma and adenocarcinoma components; cytokeratosis or keratin pearl, Bowens disease, tubular, acinar, or papillary growth patterns support ASC diagnosis. Although this case is mainly low differentiated MEC, there is a classic high differentiated MEC area (epidermoid, intermediate, and mucous cells, Fig. 1C—E), which can be diagnosed as MEC.

In conclusion, due to the lack of distinctive tumor markers and imaging features, the diagnosis of MEC requires strict histological, histochemical and immunohistochemical tests by experienced pathologists. The treatment of MEC may be hard, and more medicine-based case studies are needed to find suitable coping methods.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gendis.2021.10.002.

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