Hepatic mucinous cystic neoplasm in a male patient: A case report

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Abstract. Hepatic mucinous cystic neoplasms (MCN) are rare cystic tumors that are predominantly observed in females, with a low incidence rate in males. To date, few cases of aggressive MCN have been reported in male patients. The current study reports the case of a 74-year-old male patient who presented to Xixi Hospital with abdominal distension. Results of imaging investigations revealed a cystic lesion in the liver and histopathological examination demonstrated positive staining for caudal type homeobox 2, cytokeratin 20, postmeiotic segregation increased 2, progesterone receptor and α-inhibin, leading to a definitive diagnosis of hepatic mucinous cystadenoma. Collectively, the results of the present article demonstrated that hepatic MCN should be considered in the differential diagnosis of cystic liver lesions, including in male patients. A comprehensive evaluation that integrates clinical characteristics, and imaging and histopathological findings is essential for the optimal management of this condition.

Introduction

Hepatic mucinous cystic neoplasm (MCN), historically classified as 'biliary cystadenoma' or 'biliary cystadenocarcinoma', is a rare cystic liver tumor with an enigmatic pathogenesis. According to the 2019 World Health Organisation (WHO) classification of digestive system tumors, the diagnostic terms 'bile duct adenoma' and 'biliary cystadenocarcinoma' are no longer used. Instead, the term 'hepatic mucinous cystic neoplasm' is adopted, which is divided into three types: Mucinous cystic neoplasm with low-grade dysplasia, mucinous cystic neoplasm with high-grade dysplasia and invasive carcinoma associated with mucinous cystic neoplasm (1). Current hypotheses suggest that the origin of this tumor may involve aberrant remodeling of the embryonic ductal plate (2), or the trans-differentiation of primitive germ cells into ovarian-like stromal (OLS) cells within the periductal fetal mesenchyme, while OLS occur exclusively in females (3). MCN of the liver is rare, comprising <5% of all hepatic cystic neoplasms. Notably, this is predominantly diagnosed in females in the fourth or fifth decade of life (4). The profound disparity in incidence between biological sex, coupled with the absence of established diagnostic biomarkers, highlights the clinical challenge faced in the management of male patients with cystic liver lesions.

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Abbreviations: CDX2, caudal type homeobox 2; CK20, cytokeratin 20; ER, estrogen receptor; IPNB, intraductal papillary neoplasm of the bile duct; MCN, mucinous cystic neoplasm; MRI, magnetic resonance imaging; OLS, ovarian-like stroma; PR, progesterone receptor; MUC2, mucin 2

Key words: hepatic mucinous cystic neoplasm, male, pathology, diagnosis, liver

Case report

Patient information and clinical evaluation. A 74-year-old male patient presented to Xixi Hospital (Hangzhou, China) with a two-week history of abdominal distension and discomfort. Laboratory investigations demonstrated notable serum tumor markers, including carcinoembryonic antigen and carbohydrate antigen 19-9, and parameters indicative of healthy liver function, such as alanine aminotransferase 17 U/l (normal range, 7-40 U/l), aspartate aminotransferase 24 U/l (normal range, 13-35 U/l), alkaline phosphatase 88 U/l (normal range, 30-120 U/l) and total bilirubin 0.9 mg/dl (normal range, 0.2-1.2 mg/dl). Gastroscopic examination revealed an extrinsic compressive bulge in the gastric antrum, while findings obtained via colonoscopy were within healthy limits. Contrast-enhanced abdominal computed tomography identified a multilocular cystic lesion (8.5x5.0 cm) in the left hepatic lobe, with involvement of the common bile duct and the left portal vein (Fig. 1A). The lesion exhibited two key imaging hallmarks: i) Thickening of the nodular wall (Fig. 1B) and ii) curvilinear calcifications along the cyst wall (Fig. 1C). Upper abdominal magnetic resonance imaging (MRI) demonstrated a heterogeneous signal intensity within the hepatic parenchyma and an obscured anatomical demarcation of the hilar region (Fig. 1D). The T2-weighted sequences revealed mixed hyperintense signals (Fig. 1E). Dynamic contrast-enhanced imaging revealed mild arterial-phase enhancement of the hilar region, progressive enhancement during the portal venous phase and persistent delayed-phase enhancement. Magnetic resonance cholangiopancreatography further delineated a hilar mass

causing stricture of the proximal left intrahepatic bile ducts, resulting in post-stenotic dilation of the distal biliary branches (Fig. 1F).

Gastrointestinal endoscopy did not reveal any primary tumors within the digestive tract, ruling out the potential for liver metastasis from gastrointestinal tumors. Through imaging, a multilocular cystic lesion was observed in the left liver, characterized by thickened cyst walls and septa, in addition to nodules (Fig. 1B) and calcifications (Fig. 1C) on the walls of the cyst. However, whether the lesion was directly connected to the bile duct remained unclear, necessitating differentiation from intraductal papillary neoplasm of the bile duct (IPNB) and cholangiocarcinoma with cystic changes.

To further verify the initial diagnosis, a liver biopsy was performed. Architectural features of the cyst included a wall composed of hypocellular collagenous stroma, lined by low-grade columnar mucinous epithelium without OLS (Fig. 2A). Irregular infiltration of glandular structures with a desmoplastic reaction were indicative of stromal invasion (Fig. 2B), meeting the WHO 2022 criteria for invasive MCN (1).

Tissue analysis. For a more supportive diagnosis of MCN, further immunohistochemical tests were conducted. The tissue immunohistochemistry test was performed using specific antibodies against caudal type homeobox 2 (CDX-2; Beijing Zhongshan Jinqiao Biotechnology Co., Ltd.,), α-inhibin (Beijing Zhongshan Jinqiao Biotechnology Co., Ltd.), estrogen receptor (ER; JOINN Biologics), progesterone receptor (PR; JOINN Biologics), CK20 (Beijing Zhongshan Jinqiao Biotechnology Co., Ltd.), c-erbB-2 (Beijing Zhongshan Jinqiao Biotechnology Co., Ltd.), cytokeratin (CK)7 (Beijing Zhongshan Jinqiao Biotechnology Co., Ltd.), Ki-67 (Beijing Zhongshan Jinqiao Biotechnology Co., Ltd.), p53 (Beijing Zhongshan Jinqiao Biotechnology Co., Ltd.) and postmeiotic segregation increased 2 (PMS2; Beijing Zhongshan Jinqiao Biotechnology Co., Ltd.) (cat. nos. ZA-0520, ZM-0430, Kit-0012, Kit-0013, ZM-0148, ZM-0065, ZM0071, ZM0166, ZM0408 and ZM0407, respectively), following the manufacturer's instructions. The final immunohistochemical results were as follows: CDX-2(+), c-erbB-2(-), CK7(-), CK20(+), Ki-67(30%+), p53(-), PMS2(+), ER(-), PR(+) and α-inhibin(+). Notably, the co-expression of PR and α-inhibin (Fig. 2C and D), despite the absence of morphologically identifiable OLS, met the diagnostic criteria for MCN defined by the WHO 2022 classification (1).

Treatment and prognosis. Given the confirmed diagnosis of invasive MCN with portal vein involvement, curative intention hepatectomy was recommended. However, the patient, concerned about financial restrictions and potential side effects of surgery/chemoradiotherapy, and with a lack of confidence in treatment efficacy, declined antitumor therapy and was discharged with symptomatic medications, including digestive enzymes. However, during a telephone follow-up 6 months later, the patient was found to have passed away.

Discussion

MCN is a rare cystic malignant tumor of the liver that produces mucus and exhibits slow growth, with the potential to progress to invasive carcinoma over several years. Prior to 2005, <200 cases of MCN had been documented. At present, there are ~250 known cases of MCN; however, publications are limited due to small sample sizes and uncertainty regarding associated risk factors (5). MCNs predominantly affect the female population, while cases in male patients are considered rare (6). In the largest study to date on pancreatic MCNs, 155 of 163 patients (95%) were female, between 16 and 82 years of age, which indicates that MCNs predominantly affect women (4). Over the past decade, sporadic cases of hepatic MCN have been documented in male patients (7,8). Although a few cases of invasive pancreatic MCN in male patients have been reported, to date, no well-documented cases of invasive hepatic MCN in males have been identified in the literature (9). MCN is often asymptomatic in the early stages of the disease; however, it may cause abdominal distension, pain, dyspepsia and nausea (5).

MCN often exhibits a 'cyst within cyst' structure, with contents primarily consisting of mucus and thickened cyst walls, which may or may not be accompanied by calcification. MCN typically presents as a solitary, large, well-demarcated multilocular cystic mass, with the minority of the affected area being unilocular (6-10%). It is more commonly located in the left lobe of the liver and does not communicate directly with the bile ducts (1). MRI often demonstrates that MCN is hypointense on T1-weighted images and hyperintense on T2-weighted images, although the intensity of the signal can vary depending on the composition of the cystic fluid and the amount of mucin present. Key features of MCN include cyst wall calcification, thickened and improved septa, dilation of the upstream bile duct and mural nodules (10). Notably, a mural nodule exceeding 1 cm in size may be indicative of malignant transformation (11). Since 2010, the WHO has separated the classification of intrahepatic cystic neoplasms into MCN and IPNB. The primary distinction between these two conditions is the presence of OLS and direct communication with the bile ducts (9). The precision of preoperative imaging in diagnosing hepatic cystic lesions can be as low as 30% (12), leading to complexities in distinguishing MCN from IPNB. This underscores the critical importance of pathological analysis in accurately diagnosing hepatic MCN.

Histologically, MCN is a cystic epithelial tumor with a wall composed of three layers. The inner epithelial layer is typically columnar or cuboidal in shape (13). The middle layer consists of subepithelial OLS, which is diffusely present in ~50% of cases. This layer is composed of densely packed spindle-shaped cells with elongated nuclei and cytoplasm surrounded by collagen. Notably, the outermost layer is a fibrous capsule (5). In cases of malignant transformation, the histological appearance of these three layers changes. The epithelium forms large pseudostratified nuclei with hyperchromasia. The cells lose polarity and there are numerous mitotic figures in cases of high-grade dysplasia. Furthermore, polypoid or papillary projections are often observed (4). The intermediate layer of the stroma undergoes degeneration, exhibiting hemorrhage, calcification and necrosis. The external fibrous capsule may exhibit focal erosion that is indicative of invasive behavior. Regarding the origin of the OLS in the liver, certain researchers propose that the close proximity of the liver and gonads during embryonic development allows the migration

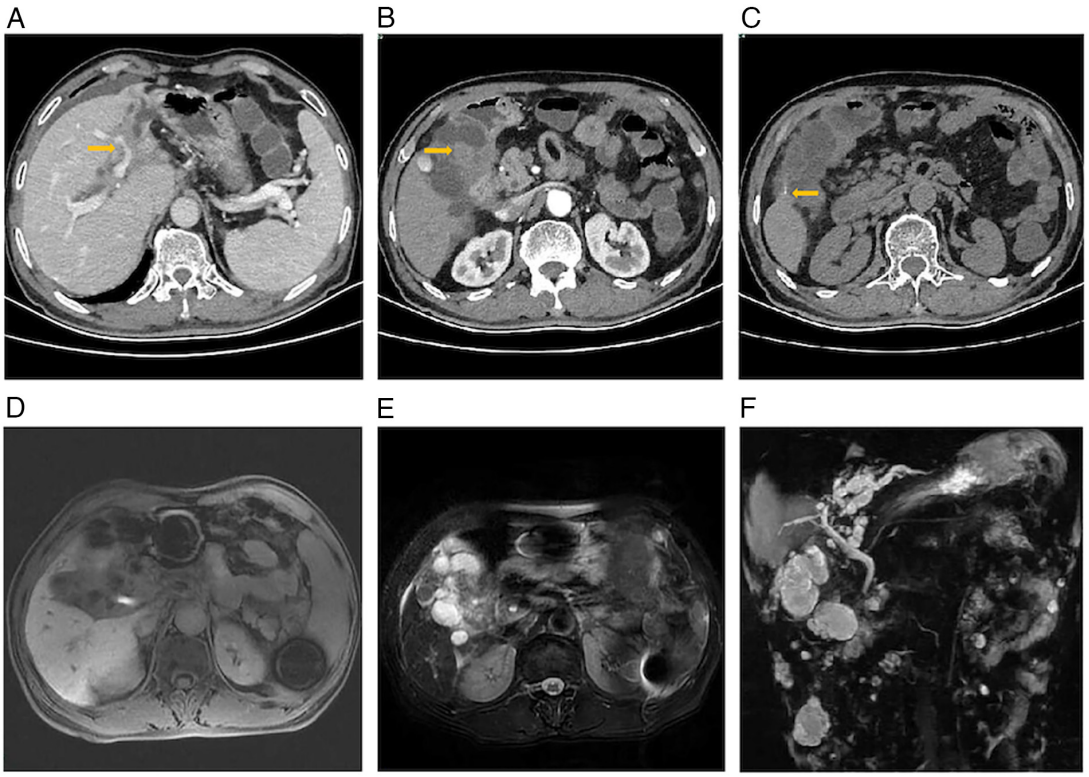


Figure 1. Imaging. (A) CT scan indicates that the common bile duct and the left branch of the portal vein at the hepatic portal are involved. The yellow arrow indicates the affected vein. (B) Enhanced CT scan revealing nodular protrusions in a portion of the cyst wall. The yellow arrow indicates the nodular protrusion. (C) Calcification was visible in a portion of the cyst wall. The yellow arrow indicates calcification. (D) On the T1-weighted magnetic resonance images, heterogeneous signals were observed in the left liver and the area of the hepatic portal, consisting primarily of iso-intense and low-intense signals. (E) T2-weighted images showed a predominantly mixed mass of high signal. (F) Magnetic resonance cholangiopancreatography revealed that the bile duct at the hepatic portal was compressed and narrowed, leading to dilation of the bile ducts in the left liver.

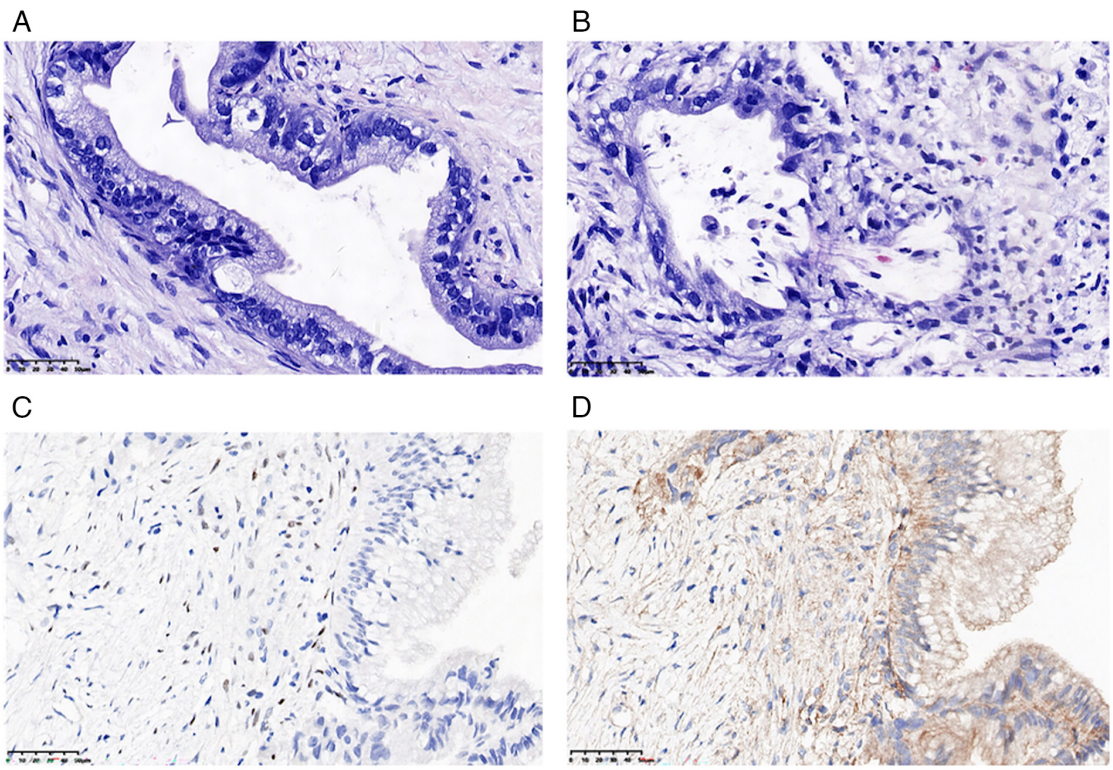


Figure 2. Pathology. (A) Under the microscope, the structure of the cyst wall reveals a cuboidal and columnar epithelium (H&E; x400 magnification). (B) Atypical glandular structures and atypical nuclei are visible (H&E; x400 magnification). (C) Immunostaining reveals a small number of cells with positive progesterone receptor expression (x400 magnification). (D) Immunostaining indicates cells expressing α-inhibin in the stroma (x400 magnification). Scale bars, 50 μm. H&E, hematoxylin and eosin.

of gonadal cells to the liver surface, leading to the formation of OLS (14). In addition, results of a previous study revealed that the peritoneal surface epithelium of the embryonic gonads was covered with bulging cells, as opposed to the typical flat epithelium; the examination of embryos suggested that during the embryonic stage, these bulging cells detach and migrate to the surfaces of nearby organs, such as the liver (15).

When MCN is a benign cystic lesion, the cyst epithelium exhibits characteristics of biliary-type epithelium, specifically CK7(+)/CK20(-)/mucin 2 (MUC2)(-)/MUC5AC(-)/MUC6(-). At this stage, the immunohistochemical characteristics of MCN are comparable with those of cysts. As the tumor progresses, the cystic epithelium exhibits gastrointestinal epithelial characteristics. Furthermore, when MCN is considered borderline or malignant, positivity rates for CK20, MUC2, MUC5AC and MUC6 are markedly increased (3). This aids in differentiating MCN from benign cysts; however, distinguishing MCN from IPNB remains challenging. IPNB also exhibits gastrointestinal epithelial characteristics, often exhibiting levels of positivity for CK20, MUC2, MUC5AC and MUC6. However, positivity for MUC1 is often only observed in the malignant phases of both tumors. ER, PR and α-inhibin are often positively expressed in the OLS of MCN; however, positive expression levels of these proteins are not observed in IPNB (16,17).

According to the results of the imaging analysis, the patient of the present study presented with a solid cystic liver tumor that invaded the hepatic portal area, accompanied by secondary dilation of the intrahepatic bile ducts in the left liver. However, the tumor exhibited no direct communication with the bile duct and no cystic dilation or nodular growth were observed within the bile duct. Furthermore, septal thickening, enhancement and wall nodules were observed in the mass, and this was accompanied by cyst wall calcification. Notably, the aforementioned radiological features are typical of MCN.

The diagnostic accuracy of preoperative imaging for hepatic cystic lesions may be as low as 30% (10); thus, further diagnostic confirmation is required using pathological analysis. Although the presence of OLS is considered key for differentiating MCN from IPNB, OLS is only present in female patients and is replaced by hyaline stroma in male patients (9). Although OLS was not observed in the present case, PR(+) and α-inhibin(+) are used to distinguish OLS from IPNB. Furthermore, the patient showed positivity for CDX2 and CK20, which is consistent with the gastrointestinal epithelial characteristics observed in MCN with an associated invasive carcinoma (3). The hallmark of IPNB is the growth of the intraductal atypical epithelial papillary and spread along the duct. Microscopic examination may reveal adjacent bile ducts with intraepithelial neoplasia or peribiliary glands within the cyst wall (17). As these factors were not observed in the present case, the diagnosis of MCN was confirmed.

Diagnostic imaging of hepatic MCN is considered to be associated with low levels of accuracy; thus, histological evaluation remains the primary method for definitive diagnosis. Immunohistochemical analysis is therefore required when there are complexities in identifying the stromal layer, mucin production is limited or the diagnosis remains inconclusive (1).

In conclusion, the diagnosis of MCN should not rely on biological sex. When evaluating patients with suspected cystic liver disease, the potential for MCN should be considered. A comprehensive assessment that integrates clinical characteristics, imaging findings and pathological features is required for accurate diagnoses in clinical practice. Furthermore, a multi-disciplinary approach involving effective communication between pathologists and clinicians is required for improved patient outcomes.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

ZZ and BW designed the study and coordinated the clinical evaluation. YZ, WP and QH participated in the diagnosis and treatment of the patient. YZ, WP and XZ were responsible for data collection, clinical interpretation and histological assessments. ZZ, WP and QH contributed to the analysis and interpretation of the laboratory and imaging data, and supervised the study. All authors participated in the writing of the original draft and figure preparation. ZZ and BW critically reviewed and revised the manuscript. XZ and QH confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by Ethics Committee Subcommittee for Scientific Research of Xixi Hospital (Hangzhou, China; approval no. 2023-090).

Patient consent for publication

Written informed consent was obtained from the patient and the patient's family for publication of this case report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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