Annals of Gastroenterology (2024) **37,** 255-265

Complex cystic liver lesions: classification, diagnosis, and management

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Abstract

Cystic liver disease has been increasingly reported in the literature, with a prevalence as high as 15-18%. Hepatic cysts are usually discovered incidentally, while their characterization and classification rely on improved imaging modalities. Complex cystic liver lesions comprise a wide variety of novel, re-introduced, and re-classified clinical entities. This spectrum of disorders ranges from non-neoplastic conditions to benign and malignant tumors. Their clinicopathological features, prognostic factors, and oncogenic pathways are incompletely understood. Despite representing a heterogeneous group of disorders, they can have similar clinical and imaging characteristics. As a result, the diagnosis and management of complex liver cysts can become quite challenging. Furthermore, inappropriate diagnosis and management can lead to high morbidity and mortality. In this review, we aim to offer up-to-date insight into the diagnosis, classification, and management of the most common complex cystic liver lesions.

Keywords Complex cystic liver lesion, hepatic mucinous cystic neoplasm, intraductal papillary neoplasm, infectious cyst, hydatid liver disease

Ann Gastroenterol 2024; 37 (3): 255-265

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Conflict of Interest: None

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Received 27 July 2023; accepted 9 January 2024; published online 6 April 2024

DOI: https://doi.org/10.20524/aog.2024.0876

Introduction

Currently affecting approximately 2.5-18% of the world population [1,2], cystic liver lesions are broadly classified into simple and complex cystic lesions. Hepatic simple cysts (HSCs), making up the majority of these lesions, are benign, rarely symptomatic [1,3], tend to remain stable in size, and seldom require treatment [1,4]. Complex liver cysts, on the other hand, include congenital, premalignant, neoplastic, infectious, and post-traumatic lesions [1,5,6]. Ultrasonography (US) as the first imaging modality, computed tomography (CT), magnetic resonance imaging (MRI), and contrast-enhanced US (CEUS), combined with clinical and laboratory data, provide useful information regarding the diagnosis and characterization of complex cystic liver lesions [1-3,7]. Since the majority of complex cysts require surgical management, difficulties in reaching an accurate diagnosis pose problems in their effective management, potentially increasing morbidity and mortality [1]. The aim of this review is to offer up-to-date insight into the diagnosis, classification, and effective management of the most common complex cystic liver lesions.

Neoplastic cystic liver lesions

Hepatic mucinous cystic neoplasms (MCNs), previously known as either biliary cystadenomas (BCAs) or biliary cystadenocarcinomas (BCACs), represent less than 3-5% of all cystic liver lesions [8-12]. Together with intraductal papillary neoplasms of the biliary tract (IPNBs), BCAs and BCACs belong to the spectrum of mucinous-secreting cystic neoplasms of the liver and biliary tract. The 2019 World Health Organization (WHO) classification of tumors of the liver and intrahepatic bile ducts highlighted a set of "essential and desirable criteria" required for the pathological diagnosis of biliary MCNs. These criteria include: i) the presence of a cystic hepatic neoplasm with no communication with the biliary tract; ii) columnar and cuboidal epithelial lining with variable mucin production; and iii) ovarian-type stroma [13]. However, this is not the case for IPNBs, which communicate with the biliary system and do not have an ovarian-type stroma. According to this classification, previous terms such as BCA, BCAC, and cystadenocarcinoma should not be used. Based on their level of neoplastic progression, MCNs are subdivided into: i) MCNs with low-grade intraepithelial neoplasia (dysplasia); ii) MCNs with high-grade intraepithelial neoplasia; and iii) MCNs with associated invasive carcinoma [13].

Noninvasive MCNs

Noninvasive MCNs are slow-growing lesions, 1.5-35 cm in size [14], commonly found in the left hepatic lobe [15,16]. Their incidence is 1-5/100,000 people, with a female preponderance and mean age of presentation at 45 years [2]. Extrahepatic and gallbladder MCNs have been reported in 10-20% of cases [3,8]. Malignant transformation to MCN with associated invasive carcinoma (previously referred to as BCAC) is estimated to be 12-30% [17-19]. Histologically, noninvasive MCNs are composed of 3 layers: a collagenous outer layer; a mesenchymal stromal layer, similar to the ovarian stroma; and a mucin-secreting columnar epithelial layer [7,13]. Similarly to normal biliary epithelium, the innermost epithelial layer of the cyst stains positive for CK-7 and CK-19 [13,18,19], with special stains (i.e., MUC5AC) applied for the identification of mucin-secreting cells. Immunohistochemistry reveals the positivity of stromal cells for estrogen receptors (ER).

Conventional US represents the initial investigation of choice for complex cystic liver lesions, defining the presence of internal septations better than other imaging modalities [3,7]. On US, these tumors often appear as ovoid, multicystic intrahepatic masses, with thickened irregular walls and multiple fine septations [1-3]. Arterial enhancement of the cyst wall, internal septa, mural and septal nodules and intracystic solid components, followed by progressive washout during the portal and late phases, are characteristic findings of MCNs on CEUS [17].

Noninvasive MCNs on CT, characteristically present as solitary, intrahepatic multicystic masses, with well-defined, thick or irregular fibrous wall, internal septa, mural nodules and rarely capsular calcifications [2,3,6,7,12]. The CT density of the tumor on unenhanced images is that of water (≤30 HU), and may vary among different intracystic loculi, because of the presence of serous, mucinous, bile-tinged fluid, cholesterol crystals, and necrotic or purulent material. Contrast enhancement is seen along the cystic wall, internal septa and mural or septal nodules [2,20].

MRI or magnetic resonance cholangiopancreatography (MRCP) has the highest sensitivity for the anatomical delineation of hepatobiliary cystic lesions [1,21], compared to CT. Typical MRI findings include the presence of a large, multilocular, fluid-containing mass, with low T1 signal, high T2 signal, thick irregular walls, and enhancing cyst wall and septa after gadolinium administration [2,3,7,21-24]. Features such as thin septations, internal hemorrhage, proteinaceous debris, fluid–fluid levels, and communication with the biliary tree with upstream biliary dilation are better demonstrated on MRI (Fig. 1) [23,24].

A specific feature in differentiating MCNs from simple septated hepatic cysts is the relationship of the septations to the outer cyst wall contour. Two studies [25,26] have demonstrated that septations arising from external macrolobulations or sites of cyst wall concavity were 91-100% specific for HSCs, whereas septations arising from cyst wall sites other than the external macrolobulations or concavity have 56-93% specificity for MCNs. Fine-needle aspiration is not recommended for MCNs, given the risk of tumor dissemination. Elevated levels of CA 19-9 and CEA can vary widely, and are thus of limited clinical utility [7,27]. TAG-72 (also referred to as CA72-4) in cyst fluid has shown the best diagnostic capability for discriminating between malignant cysts (>25 U/mL) and HSCs [28]. The difficulty in differentiating noninvasive from invasive MCNs and their considerable malignant transformation rate mandate complete surgical removal as the treatment modality of choice.

MCNs with associated invasive carcinoma

Invasive (previously known as BCACs) in contrast to noninvasive (previously known as BCAs) MCNs, occur more frequently in old, male patients. They account for approximately 6% of all MCN cases, and are identified in larger tumors, with a tubular or tubulopapillary architectural pattern. However, it is difficult to differentiate between invasive and noninvasive MCNs based on imaging alone [1,2,7,20,23,26]. Clinical manifestations, demographic variables (age, sex), and liver function tests (LFTs) may prove useful in this regard. LFT elevation in invasive MCNs occurs secondary to invasion of the adjacent biliary tree, while serum CEA and CA 19-9 levels are of moderate predictive value in this setting [29].

In terms of imaging, both neoplasms appear as solitary, intrahepatic multilocular cystic tumors. Internal septations without nodularity are more suggestive of noninvasive MCNs. Mural or septal nodules, as well as irregular cyst wall thickening, although increasing the likelihood of malignancy,

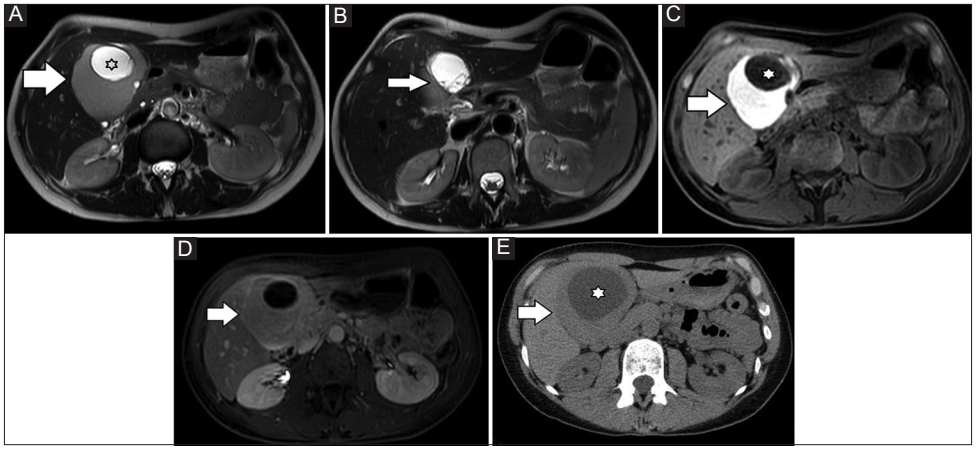

Figure 1 Mucinous cystic neoplasm in a 41-year-old woman. Transverse T2-weighted (A, B) and T1-weighted images (C), depict a large multicystic lesion (arrow), in the left liver lobe. The mass is well-defined, with a central part (asterisk), appearing hyperintense on T2WI and hypointense on T1WI, a finding suggestive of serous content surrounded by high T1-signal material, corresponding to mucinous content (C). (D) Transverse delayed fat-suppressed post-contrast T1-weighted image shows cystic wall and septal enhancement. (E) Unenhanced computed tomography (CT) image in the same patient demonstrates a lesion with a cystic part of water density (asterisk) (mean CT density: 10 HU) and an isodense surrounding part (arrow), with a mean CT density of 45 HU

may also be detected in benign MCNs. However, the presence of nodules greater than 10 mm in diameter and/or a significant solid component, intracystic debris and coarse calcifications increase the likelihood of an invasive MCN [1,2,7,20,23,26].

Molecular studies have shown that *KRAS* mutations, hedgehog and Wnt pathway upregulation, and downregulation of T-helper -1 and -2 pathways, are some of the molecular mechanisms potentially driving the gradual progression of benign biliary MCNs into invasive lesions [13,19].

IPNBs

The term IPNB was introduced in 2001 by Chen *et al* [30], and was defined as an epithelial tumor of the bile ducts, characterized by the presence of prominent, often multifocal (up to 50%) [30], papillary or villous epithelial lesions within the bile duct lumen, with or without (2/3 of cases) mucin production [31], in the presence of bile duct dilation [2,31]. They comprise entities previously known as biliary papillomas and biliary papillomatosis, and can develop anywhere along the biliary tree, including intrahepatic (69%), extrahepatic (22%) and hilar (9%) sites [31]. IPNBs are characterized by communication with the bile ducts and downstream biliary dilation secondary to luminal mucin production, rather than upstream dilation, which is more frequently observed in MCNs causing external compression [32,33]. In IPNBs with predominantly papillary proliferation, biliary dilation can occur secondary to tumor mass effect. For unclear reasons, left-sided bile ducts are most commonly affected [7].

IPNBs account for about 10-15% of bile duct tumors [34]. Commonly reported symptoms include right upper quadrant pain (35-88%), recurrent cholangitis (5-59%), and obstructive jaundice (20-36%). Laboratory workup may reveal abnormal LFTs and bilirubin. Increased serum CA 19-9 has limited specificity, since it is frequently correlated with multiple inflammatory or neoplastic conditions causing cholestasis or cholangitis [35-37].

IPNBs and biliary intraepithelial neoplasms are the 2 principal early/pre-invasive lesions leading to invasive cholangiocarcinomas [31,38]. Based on their malignant potential, they are further subdivided into low-grade and high-grade dysplastic lesions, as well as IPNBs associated with invasive carcinoma. P53 and p16 inactivation, as well as KRAS mutations, occur at the early stages of IPNB development, while loss of SMAD4/DPC4 is observed during later stages of disease progression. Nuclear β-catenin expression and *GNAS* mutations have also been detected in some instances [38,39].

Transabdominal ultrasound is quite helpful in depicting biliary dilation and hepatolithiasis, but has relatively limited sensitivity (41%) in diagnosing IPNBs. In this regard, further imaging with either contrast-enhanced CT (50% sensitivity), or MRI/MRCP (showing the highest sensitivity: 65.5%) are required for more precise diagnosis and staging [31]. Endoscopic retrograde cholangiopancreatography can depict intraluminal lesions as irregular filling defects within the bile ducts. A dilated ampulla of Vater with "fishmouth" appearance, and visible mucin draining via its orifice, are additional endoscopic features of mucin-producing IPNBs. EUS assesses the depth of infiltration into the bile duct wall, while also depicting irregularly enlarged hepatoduodenal lymph nodes. Cholangioscopy offers direct visualization of the solid IPNB portion, detecting lesions not seen on initial imaging in up to one third of cases [31], while also allowing for confirmatory biopsies. Whole-body PET/CT may have a role in questionable IPNBs, where increased FDG uptake raises the suspicion for underlying malignancy [31].

There are 4 distinct radiologic patterns of IPNBs, depending on the size and morphology of the intraductal mass, degree of mucin secretion, and tumor location [31] (Fig. 2).

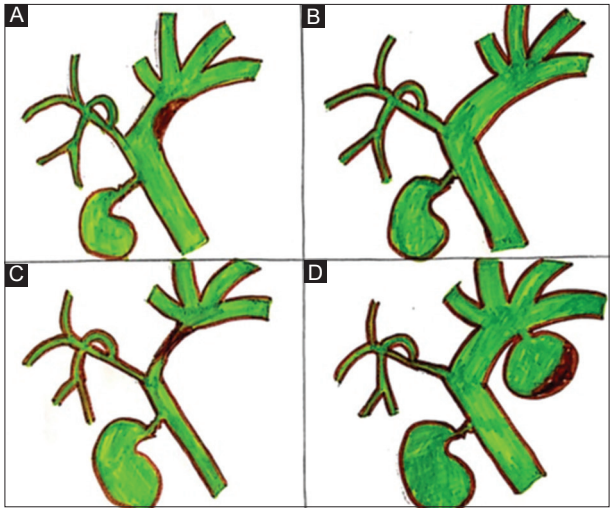

Figure 2 Intraductal papillary neoplasms of the biliary tract with 4 different radiologic patterns: (A) intraductal mass (brown) with proximal and distal ductal dilation; (B) disproportionate dilation without mass; (C) intraductal mass with proximal ductal dilation; (D) focal cystic dilation with a papillary mass

i) Intraductal mass with proximal ductal dilation (type 1 IPNBs)

In non-mucin-secreting IPNBs, the intraductal mass may cause ductal obstruction with upstream biliary dilation. On arterial phase CT images, intraductal mass-forming IPNBs tend to be iso-enhancing compared to the adjacent liver parenchyma. Delayed phase images, however, may assist in differentiating IPNBs from cholangiocarcinomas, since IPNBs tend to "wash out", owing to the paucity of fibrous tissue within the cellular fibrovascular stalk [31]. Quite the opposite is true for cholangiocarcinomas, which are typically associated with delayed, gradual enhancement due to their high fibrous content. On T2-weighted MR sequences, type 1 IPNBs usually show an intermediate-to-low signal papillary pattern, which can be easily identified against the high T2 signal intensity of background bile. The presence of markedly low diffusion coefficients in diffusion-weighted imaging should raise the high possibility of IPNBs associated with invasive carcinoma [31,40].

ii) Disproportionate dilation without visible mass (type 2 IPNBs)

Mucin-secreting IPNBs without a visible intraductal mass are very challenging to identify, since the only radiologic finding could be a segmental or lobar bile duct dilation on MRCP. To localize the tumor, the hepatic segment with the most prominent biliary dilation and associated atrophy should be evaluated first. Hong *et al* [41], reported that intraductal linear or curvilinear hypointense striations within a dilated bile duct (so-called "thread sign") are highly specific for IPNB (99-100%), yet with a sensitivity as low as 45-53%.

iii) Intraductal mass with proximal and distal ductal dilation (type 3 IPNBs)

This is the most common subtype of IPNB [2], classically appearing as an intraductal cauliflower-like papillary tumor, associated with both upstream and downstream biliary dilation secondary to mucin secretion [7].

iv) Focal cystic dilation with papillary mass (type 4 IPNBs)

In type 4 IPNBs, mucin overproduction leads to increased intraductal pressure and aneurysmal biliary dilation or cystic dilation of peribiliary glands [7,42]. These cystic-type IPNBs present as multilocular cystic masses with a "bunch of grapes" appearance and enhancing mural nodules (Fig. 3). Type 4 IPNBs, which closely resemble MCNs, can be differentiated on the basis of communication between the cystic lesion and the bile ducts, best depicted on MRCP sequences [2,31]. Similarly, MCNs in contrast to cystic-type IPNBs are not accompanied by biliary dilation. Gadolinium-based agents, excreted into the lesion on the hepatobiliary phase, are quite helpful in this regard [31,42]. Apart from MCNs, the differential diagnosis should include complicated hepatic cysts, localized Caroli disease, and more rare cystic hemangiomas, lymphangiomas, hepatic foregut cysts, mesenchymal hematomas or teratomas [1,31].

It should be noted that ductal invasion by HCC and intraductal hepatic metastases have to be excluded during the workup for types 1, 3 and 4 IPNBs. The former presents as a hypervascular parenchymal mass with delayed washout in patients with risk factors for HCC. The latter is associated with a contiguous parenchymal mass and a history of primary malignancy, usually of colorectal origin.

IPNBs display microscopic fibrovascular cores or tubulopapillary formations within the bile ducts. The epithelium may be of pancreatobiliary, intestinal, gastric or oncocytic type, with various degrees of atypia. According to their histopathologic subtype, IPNBs may express specific mucin core proteins, such as MUC5AC and MUC6 in the pancreatobiliary and gastric type, MUC-1 in the pancreatobiliary subtype, and MUC2 in intestinal type cells. The neoplastic stroma is fibrous and lacks the ovarian-like morphology of MCNs. The majority of the carcinomas arising from IPNBs are pancreatobiliary type cholangiocarcinomas, while mucinous carcinomas are usually associated with intestinal type tumors [31]. IPNBs with invasive characteristics follow the staging of intrahepatic cholangiocarcinomas, with a better prognosis, determined by the depth of invasion as well as the proportion (%) of the invasive component [43].

Management options (HSCs vs. mucinous-secreting cystic neoplasms of the liver and biliary tract)

Treatment may be indicated for symptomatic or questionable HSCs. Open or laparoscopic fenestration ("unroofing") is the first-line treatment to drain an HSC in the peritoneal cavity [7,44], resulting in symptom reduction

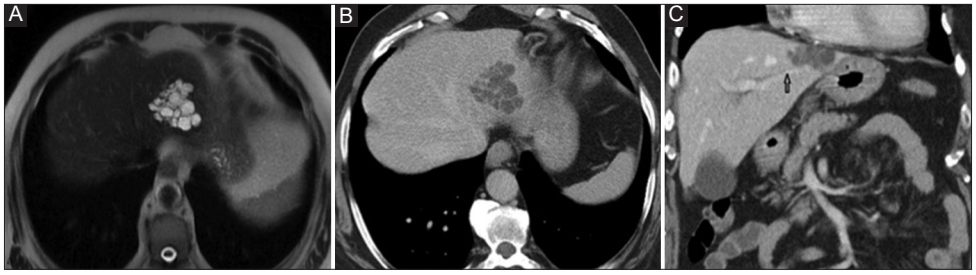

Figure 3 (A) T2-weighted axial magnetic resonance imaging: a well-defined multilocular "bunch of grapes-type" intrahepatic mass is depicted, containing high intensity fluid content and multiple internal septa. (B) Axial contrast enhanced computed tomography (CT): the multilocular cystic lesion shows thick internal septa with persistent delayed phase enhancement. (C) Coronal portal phase CT: a well-defined multilocular cystic mass is depicted in the left liver lobe. This is in close proximity to the hypodense linear left intrahepatic biliary duct (arrow)

in 92% of cases [3,45]. Laparoscopic fenestration combined with marsupialization appeared to be safe and effective in patients with HSCs measuring >15 cm in diameter [46], with a single recurrence recorded during 41 months of follow up. Endoscopic transgastric cyst drainage [47] is an attractive treatment option, eliminating the need for incisions. However, it is limited to superficially located left-sided liver cysts, unless the procedure is assisted laparoscopically.

Sclerotherapy is a simple, safe and efficacious treatment indicated in patients with poor performance status. During this procedure, a sclerosing agent (dehydrated alcohol or tetracycline) is injected into HSCs after complete aspiration of their content [45,48]. In a multicenter study comprising HSCs >5 cm in diameter, complete clinical response was 55% at 6 months [45], while lesser responses have been observed with complex cysts containing hemorrhagic or large amounts of intracystic debris [45]. If malignancy is suspected, liver resection with clear margins is required.

Due to the inherent limitations of preoperative diagnostic tools, all suspected biliary MCNs should ideally be surgically removed with negative margins. Especially in MCNs with associated invasive carcinoma, the gold standard of treatment is radical resection with a wide (>2 cm) surgical margin. Pathological staging of invasive MCNs follows the staging of intrahepatic cholangiocarcinomas [3]. However, they present a notably favorable prognosis compared to other hepatic malignancies, since they exhibit less aggressive clinical behavior, with slow growth and rare metastases [3]. In a retrospective study by Jwa *et al* [49], no tumor recurrences were observed in patients with MCNs undergoing complete surgical removal. Postoperative 1-, 3- and 5-year survival rates in patients bearing invasive MCNs were 100%, 100%, and 75.0%, respectively. Optimal prognosis is expected only if complete (R0) resection is contemplated [49]. Klompenhouwer *et al* [50] reported a 5% recurrence rate for MCNs following resection or enucleation, and up to 100% post-fenestration. In a literature review analyzing 25 studies that included 103 patients with MCNs [51], the main indication to choose enucleation over liver resection was a large cyst located in a central liver portion. Data review demonstrated a 0% recurrence rate, no postoperative deaths, and no late occurring malignancies. The authors concluded that MCN enucleation is a safe and effective option for patients who cannot tolerate major hepatectomy.

Surgical resection is the mainstay of treatment for IPNBs. The extent of surgical resection depends on the tumor location, the degree of biliary tract involvement and patient suitability. Most patients are sufficiently treated with radical surgical resection, which includes hepatectomy with or without bile duct resection [42,52]. In extreme cases with more aggressive IPNBs and positive resection margins, major hepatectomy or orthotopic liver transplantation, with or without pancreaticoduodenectomy, may be performed. IPNBs undergoing curative surgical resection present a significantly better prognosis compared to cholangiocarcinomas, with 5-year disease-free survival as high as 81% [31,40,42]. Positive resection margins, positive lymph nodes, tumor invasion ≥5 mm and invasive component ≥10% are all associated with a poorer prognosis [31]. Taking into account the incidence of invasiveness and metastases in patients with IPNBs, and hence the high possibility of disease recurrence, regular postoperative follow up with short-interval imaging is recommended [53].

Infectious cysts

Bacterial, fungal and amoebic liver abscesses and hepatic hydatid cysts are among the differential considerations for complex liver cysts.

Liver abscess

Pyogenic liver abscesses develop secondary to ascending cholangitis, hematogenous dissemination, or pylephlebitis following intra-abdominal infections such as acute appendicitis or diverticulitis [54]. The incidence is higher in middle-aged or elderly patients who present with low-grade evening fever, right upper quadrant pain, fatigue, tender hepatomegaly, and elevated white blood cell count [55].

Infectious abscesses on contrast-enhanced CT demonstrate a peripherally enhancing rim surrounding a central low attenuation area, and then an outer low attenuation zone secondary to perilesional parenchymal edema, producing the characteristic "double target" sign [56]. The presence of gas within an abscess is a strong indication of gas-producing

species. Treatment options for pyogenic liver abscesses include antibiotic therapy and percutaneous or open drainage [57]. Long-term antibiotic therapy alone (>3 weeks) can be applied in patients with single small (<3 cm) liver abscesses. Percutaneous catheter drainage combined with antibiotics has been associated with success rates exceeding 97% [58] and more rapid clinical improvement. Ahmed *et al* [59] studied 40 patients with pyogenic liver abscesses measuring >10 cm in diameter. Percutaneous drainage was successful in 98% of patients, with 1 patient requiring subsequent open drainage and 3 patients undergoing secondary percutaneous drainage procedures. Complications (mostly minor) were observed in 25% of patients and there was 1 death. Open surgical drainage comes into play for patients who fail to respond to the above treatment, as well as in patients with peritonitis or complex, septated, and multiloculated abscesses.

Amoebic abscess is the most common extracolonic manifestation of amebiasis [60]. Patients present with hepatomegaly, right upper quadrant pain, diarrhea, history of travel to an endemic area and positive serology. Unlike pyogenic abscesses, amoebic abscesses rarely need therapeutic drainage and are quite effectively managed with oral metronidazole administered for 7-10 days. Percutaneous or surgical drainage may be necessary in up to 15% of cases, to manage enlarging superficial abscesses (with high risk of rupture), bacterial superinfections, or when metronidazole treatment fails.

Candida abscesses are usually encountered in immune-compromised patients. CT scans show multiple low-attenuation lesions, with a typical enhancing rim and frequent involvement of the spleen [61]. In patients who fail to improve after drainage and broad-spectrum antibiotics, antimycotic therapy should be considered early, before the onset of fungemia.

Echinococcal cysts (ECs)

Hydatid liver disease is an endemic parasitic infection caused by metacestodes (larval stage) of *Echinococcus granulosus* following consumption of contaminated food [1,7]. The ingested larvae hatch in the small intestine, penetrate into the bloodstream and migrate to the liver and lungs (which constitute their main target organs) or other tissues, where hydatid cysts develop [62]. Each cyst consists of an outer pericyst (or adventitial) layer, a middle-laminated membrane or ectocyst, and an inner germinal layer. Together the ectocyst and the inner germinal layer are referred to as the endocyst. Daughter cysts develop on the periphery of a mother cyst, secondary to germinal layer invaginations portending to ECs the appearance of complex liver lesions. ECs remain subclinical for months to years [63,64]. Clinical manifestations include right upper quadrant pain, anorexia, obstructive jaundice and pruritus [65]. Cyst rupture or leakage is associated with a severe immunoglobulin E-related immunologic reaction, manifesting with fever, pruritus and eosinophilia, frequently leading to a life-threatening anaphylactic reaction [66]. Secondary hydatidosis, sepsis and acute cholangitis have also been described as complications following EC rupture [67,68]. ECs communicating with the biliary tree are usually inactive. Yet on rare occasions, such long-standing ECs tend to expand extrahepatically, invading adjacent viscera of the upper abdomen.

EC mortality in endemic countries, as well as in countries where immigrants from these countries arrive, is estimated to be 2-5% [7], highlighting the role of accurate diagnosis. Diagnosis can be reached by means of serological testing combined with appropriate imaging. Anti-echinococcal antibody assays [63,69] have a sensitivity rate as high as 97% [70], but cannot distinguish between active or past infections, while in 30-40% of patients no antibodies are detectable. Echinococcal antigen assays present an excessively broad sensitivity range (33-85%) [71,72], currently precluding their utilization in clinical practise. In this respect, EC confirmation is provided by means of imaging, as proposed by the WHO-Informal Working Group Classification on Echinococcus (WHO-IWGE) [73].

US is the initial imaging modality in the assessment of the number, location and internal structure, and possible complications of ECs, while it can also be applied for patient follow up [74]. In addition, it can guide therapeutic decisions by classifying ECs into active, transitional or inactive [75-78].

In 2001, the WHO-IWGE standardized a classification system for cystic echinococcosis (CE) [78], to replace pre-existing systems and facilitate a natural grouping of ECs into 3 relevant groups: active (CE1 and CE2), transitional (CE3), and inactive cysts (CE4 and CE5). CE1 includes unilocular cysts, with uniform anechoic content, visible wall and "snowflake sign", while CE2 includes multilocular, multiseptated cysts, with daughter cysts and "honeycomb sign". Class CE3 includes cysts that are thought to be degenerating (transitional group). CE3 transitional cysts are further subdivided in CE3a unilocular fluid collections, with a floating membrane of detached endocyst ("water-lily sign"), and CE3b, predominantly solid EC with daughter cysts. Class CE4 includes cysts with heterogeneous hypoechoic or hyperechoic degenerative content and daughter cysts, and class CE5 includes cysts with a thick calcified wall [78].

CT and MRI are both helpful in investigating subdiaphragmatic ECs, as well as detecting ECs disseminated in extra-abdominal locations. CT aids in confirming EC diagnosis, revealing the location and depth of the cyst within the liver parenchyma, the presence of calcified walls (in 50% of cases) and daughter cysts (identified in approximately 75% of patients), while also assisting in surgical decision making [3,74,79].

Type I ECs appear on CT as well-defined, unilocular, non-enhancing cystic lesions with water density, simulating a simple liver cyst [3,74,80]. Type II ECs are further sub-classified as: cystic lesions with round daughter cysts, arranged at the periphery, often with CT attenuation lower than that of the mother cyst (type IIA); larger daughter cysts of irregular shape, occupying almost the entire mother cyst leaving hyperdense fluid in-between, creating a "rosette" appearance (type IIB); and hyperdense, round or oval intrahepatic mass with scattered calcifications and occasional daughter cysts (type IIIC) (Fig. 4A,B). Cyst calcifications appear hyperdense on CT, and are usually curvilinear or ringlike, involving the pericyst, with complete calcification occurring in later stages of the disease [3,74,80].

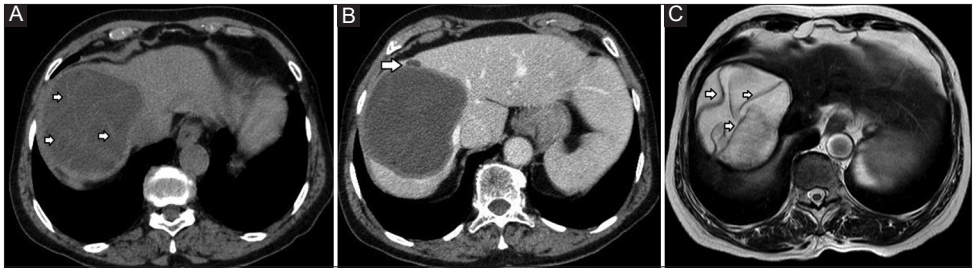

Figure 4 Hepatic echinococcal cyst in a 40-year-old woman. Transverse (A) unenhanced and (B) contrast-enhanced computed tomography images demonstrate a large, well-defined cystic mass in the right liver lobe. Internal hyperdense floating membranes (small white arrows) are detected within the lesion and a small round daughter cyst (large white arrow) is seen peripherally. (C) Axial T2-weighted image of the same patient. The lesion is hyperintense, with detached membranes of low signal (small arrows) floating within the cyst. The cyst is surrounded by a hypointense halo, corresponding to the pericyst

Typical features of ECs on MRI may include: i) a low-signal-intensity rim ("rim sign") on T2WI, representing the combined pericyst and endocyst layers of an intact cyst; ii) a markedly hyperintense hydatid matrix on T2WI ("hydatid sand"); iii) the daughter cysts appearing isointense to the mother cyst on T2WI and hypointense or isointense to the hydatid matrix on T1WI and T2WI respectively, when viable; iv) the detached floating EC membranes, seen as dark on both T1WI and T2WI ("serpent sign" or "snake sign" (Fig. 4C); and v) the calcifications, appearing as areas of signal dropout [3,74,81,82].

CT represents the examination of choice for the detection of biliary and/or vascular involvement, cyst wall rupture and superinfection. Changes in EC architecture, biliary dilation, presence of air, air-fluid level, or fat-fluid level within the cyst are nonspecific signs of intrabiliary rupture [83]. T2-weighted MRI sequences and MRCP are similarly useful in diagnosing intrabiliary EC rupture. A poorly defined cystic lesion, a hyperenhancing rim, patchy heterogeneously enhancing areas in the vicinity of the lesion, and internal gas or air-fluid levels within the cyst combined with the appropriate clinical scenario are CT findings highly suggestive of EC superinfection [83].

Type I ECs, and biliary MCNs share many common radiologic characteristics with HSCs. When managing patients with unilocular cystic liver lesions, one should bear in mind that rapidly growing symptomatic cysts need to be differentiated both from MCNs and ECs, thus anti-echinococcal antibodies should always be sent along with the remaining work up, especially in endemic areas or when immigrants from these areas are involved.

The optimal therapeutic approach for the management of hepatic ECs depends on the extent of organ involvement, the number and size of cysts, the presence of communication with the biliary tree, simultaneous bacterial contamination and/or intracystic hemorrhage. One can choose between 3 different treatment modalities: a) systemic chemotherapy with mebendazole/albendazole; b) surgical approaches, ranging from deroofing to major hepatectomy; and c) percutaneous US guided "puncture, aspiration, injection and re-aspiration" (PAIR) [84]. Small ECs (<5 cm) can be managed with antihelminthics and clinical observation. In a study evaluating this "watch and wait" strategy [85], 97.4% of ECs remained inactive over a 2-year period, although a longer follow-up period needs to be fully evaluated.

Surgical interventions can be open or laparoscopic, conservative or radical [62,82]. Conservative techniques include drainage, and unroofing, with or without omentoplasty. In fenestration, the cyst is opened and its content is aspirated following injection of hypertonic saline.

Radical procedures include total pericystectomy [86] and minor or major hepatectomy. A benzimidazole agent is always administered prior to any type of surgery to sterilize the cyst and reduce the risk of anaphylactic reaction [62]. PAIR involves puncture, aspiration of the cyst, injection of hypertonic saline and/or absolute alcohol, and re-aspiration. It is indicated for ECs 5-10 cm in diameter, in poor surgical candidates or in patients who have failed previous surgical interventions [87]. It is best performed under continuous US or CT guidance with benzimidazole coverage. A study by Chen *et al* [88], showed a 98.7% cure rate in patients undergoing laparoscopic intervention, and 97.5% in patients receiving PAIR plus chemotherapy. Follow up is recommended initially every 6 months for the first 2 years, and then once a year, depending on the clinical setting [89].

Inflammatory (peribiliary) cysts

Peribiliary cysts are multiple, bilateral cystic lesions (0.2-2.5 cm) that develop secondary to disturbed periportal blood flow and resultant periportal inflammation in cirrhotic livers, or as a result of genetic changes accompanying hereditary fibrocystic diseases [90]. These lesions are located predominantly around the hepatic confluence, with no communication with the biliary tree. They do not require any treatment. Nevertheless, correct diagnosis is essential, since misdiagnosis of peribiliary cysts as malignant lesions can cause unnecessary denials or delays in patients with end-stage liver disease listed for liver transplantation.

Complicated (hemorrhagic or infected) HSCs

Intracystic hemorrhage (the most frequent complication of HSCs) or HSC infection lead eventually to the development

of complex cystic lesions, which are usually indistinguishable from neoplasias. Clinical manifestations include pain and fever, while on US they appear hypoechoic with a thick wall, debris, and distal acoustic enhancement without internal vascularity. CT imaging of hemorrhagic cysts varies from HSCs with internal hemorrhagic components appearing as "flame-like" prominences [91], to more complex cystic masses with a thick fibrous capsule, internal septations and mural nodularity. Infected HSCs on CT present enhanced wall thickening, fluid-fluid level, or intracystic gas bubbles. Hemorrhagic or proteinaceous content does not enhance on MRI. However, hemorrhagic cysts are hyperintense on both T1- and T2-weighted sequences in the acute setting [92]. Some months later they may appear hyperintense on T1W imaging, while septations, mural nodularity, and internal debris may also be present [3]. Ultrasound and MRI are more accurate in the diagnosis of intracystic hemorrhage. CT is preferred to detect active extravasation of hemorrhagic content in the abdominal cavity in the event of cyst wall rupture [93]. Hemorrhagic cysts are usually managed conservatively. Anticoagulants and antiplatelets are discontinued temporarily and restarted 7-15 days or 3 days, respectively, after the cessation of active bleeding. Embolization or surgery are indicated in cases of non-contained HSC rupture or hemodynamic instability [93].

^{18}FDG PET-CT shows increased FDG uptake of the cyst lining relative to normal hepatic parenchyma and can be used to support the diagnosis of infected cysts in difficult cases [93,94]. Fluoroquinolones and third-generation cephalosporins are the standard of care for infected hepatic cysts [95]. Initial parenteral administration, followed by a prolonged course of oral antibiotics (4-6 weeks in total), is recommended. However, the majority of infected cysts require additional percutaneous drainage to achieve definitive treatment [93,96]. The main indications for percutaneous drainage of infected cysts are: cyst diameter >5 cm; no response to antibiotics after 48 h; presence of gas within the cyst on CT or MRI; and vulnerable immunocompromised patients [93].

Uncommon and congenital liver cysts

Ductal plate malformations, also known as fibropolycystic liver diseases, represent a unique spectrum of pathological abnormalities that are caused by an insult to the embryonic

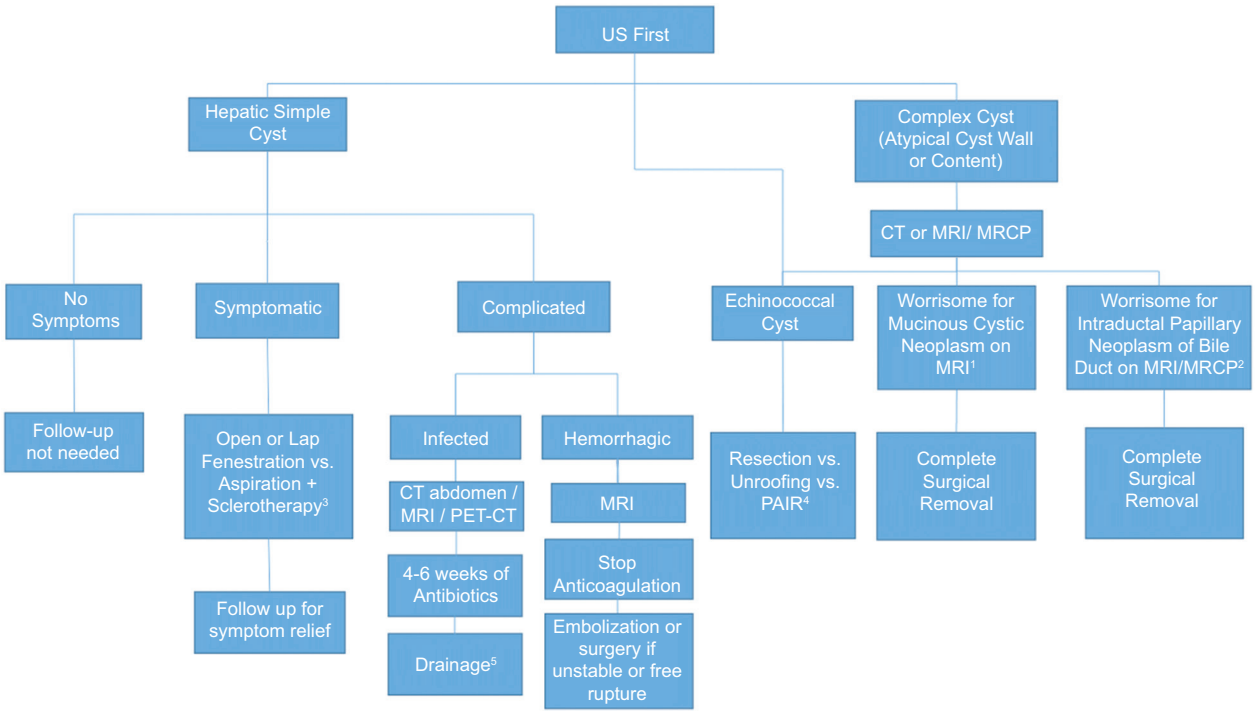

Figure 5 Management algorithm for cystic liver lesions

[1]A combination of ≥1 major (thick septation or nodularity) and ≥1 minor (upstream biliary dilation, thin septation, internal hemorrhage, perfusional change, <3 coexistent cysts) criteria [93]

[2]Focal cystic dilation communicating with the bile ducts + solid component

[3]Aspiration and sclerotherapy as second choice mainly for poor surgical candidates

[4]Percutaneous aspiration injection re-aspiration (PAIR) for echinococcal cysts 5-10 cm in diameter, poor surgical candidates, or failed previous surgical intervention

[5]Cyst diameter >5 *cm*, no response to antibiotics after 48 *h*, presence of gas within the cyst on abdominal computed tomography or magnetic resonance imaging, and vulnerable immunocompromised patients [93]

US, ultrasonography; CT, computed tomography; MRI, magnetic resonance imaging; MRCP, MR cholangiopancreatography

ductal plate development. As a result, congenital cystic lesions tend to develop in intra- or extra-hepatic bile ducts, predisposing for pancreatitis, cholangitis, lithiasis and malignancy. Depending on the timing of ductal plate insult, different congenital cystic lesions develop, including biliary hamartomas; autosomal dominant polycystic liver disease (in the presence of >20 hepatic cysts), Caroli disease (type V lesions based on Todani classification), and choledochal cysts [1,97]. These lesions need to be considered in the differential diagnosis of complex cystic liver lesions when they are complicated with hemorrhage, bacterial superinfection, or intracystic development of neoplastic lesions, and should be treated as previously discussed. Polycystic liver disease with compression on the bile ducts, the hepatic veins, the inferior vena cava, the portal vein (causing portal hypertension) or adjacent viscera may dictate the need for open or laparoscopic fenestration of multiple liver cysts, or hepatectomy in appropriate surgical candidates [98]. Orthotopic liver transplantation should be reserved for severe hepatic decompensation, ascites, malnutrition, vascular occlusion, or when resection fails or is deemed inappropriate.

Concluding remarks

Complex cystic liver lesions are increasingly being recognized in asymptomatic individuals or during workup for non-specific abdominal symptoms, leading patients to seek surgical attention. They encompass a spectrum of disorders ranging from non-neoplastic conditions to benign and malignant tumors. These complex cystic liver lesions pose multiple diagnostic and therapeutic dilemmas to hepatobiliary specialists (radiologists, gastroenterologists, pathologists, hepatologists and surgeons). Liver cyst characteristics that can assist with their classification, include presence of septa, enhancing thickened wall, mural consistency/nodularity, calcifications, and quality of cystic fluid with or without debris. When a high index of suspicion for underlying malignancy is present, cases should be discussed in a multidisciplinary tumor board meeting. If malignancy or high-grade dysplasia is anticipated, surgical options include radical resection and enucleation, according to cyst location and the patient's performance status. When imaging characteristics are atypical or inconclusive, regular short-interval monitoring with high resolution imaging should be entertained (Fig. 5) [93]. Extensive research into the pathogenesis and progression of complex cystic liver lesions is currently underway. Ongoing studies will hopefully bring forward a set of clinically relevant molecular markers to help improve the diagnosis and classification of these lesions.

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