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INVITED REVIEW

Early detection of intrahepatic cholangiocarcinoma

Mami Hamaoka[1] · Kazuto Kozaka[1] · Osamu Matsui[1] · Takahiro Komori[1] · Takashi Matsubara[1] · Norihide Yoneda[1] · Kotaro Yoshida[1] · Dai Inoue[1] · Azusa Kitao[1] · Wataru Koda[1] · Toshifumi Gabata[1] · Satoshi Kobayashi[2]

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Abstract
Cholangiocarcinoma (CC) is a malignant tumor which arises from the biliary epithelium and most cases represent adenocarcinoma. CC can be classified into intrahepatic CC (ICC), perihilar CC, and distal CC, based on the site of anatomic origin. The incidence of ICC is increasing in both Western and Eastern countries, while that of extrahepatic cholangiocarcinoma remains fairly stable. ICC infiltrates into adjacent nerves and lymphatic vessels, resulting in progressive disease with a poor prognosis; thus, early detection of ICC is critical for achieving better outcomes and providing better patient care. However, it is difficult for clinicians to detect an ICC, especially in its early stage. Different from hepatocellular carcinoma, the lack of surveillance system for the high-risk group of CC does not allow for a reliable screening examination. In this context, for early detection and diagnosis of ICC, radiologists need to know predisposing conditions that can lead to the development of ICC, such as chronic biliary or hepatic inflammation, primary sclerosing cholangitis, congenital biliary diseases, and other conditions. In this article, we discuss and illustrate the radiologic features of ICC with special attention to early disease stages and of predisposing conditions of ICC.

Keywords Intrahepatic cholangiocarcinoma · Diagnoses, computer-assisted · Computed tomography, multidetector · Imaging, magnetic resonance · Magnetic resonance cholangiopancreatography

Introduction

Cholangiocarcinoma (CC) can be classified into intrahepatic CC (ICC), perihilar CC, and distal CC, based on the site of anatomic origin (Table 1) [1]. Among them, the incidence of ICC is increasing in both Western and Eastern countries, while that of extrahepatic CC has remained fairly stable [2]. Patients with extrahepatic CC usually present with jaundice, dark urine, pale stools, pruritus, malaise, and weight loss even in early-stage disease, making diagnosis relatively straightforward using imaging such as ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI). However, it is difficult to diagnose ICC in its early stage because patients with ICC present with no symptoms or nonspecific symptoms including abdominal pain, appetite loss, weight loss, malaise, and night sweats—even those with advanced stage disease [3]. In addition, there is no established surveillance system for ICC in specific patient groups, which differs from patients at high risk for hepatocellular carcinoma (HCC) such as those with chronic, viral, or autoimmune hepatitis [4]. Although the cause of most CC is unknown, there are several risk factors. Chronic biliary inflammation caused by primary sclerosing cholangitis (PSC), hepato-choledocholithiasis, liver flukes, and other conditions can induce neoplastic change of the bile duct, and genetic cellular events in the hyperplasia–dysplasia–carcinoma process have been proposed as risk factors [5]. In addition, chronic hepatitis has recently been recognized as one of the important risk factors of ICC [2, 6, 7] (Table 2).

ICC infiltrates easily into surrounding interstitial connective tissue which contains nerves and vessels, often resulting in progressive disease at the time of detection and, thus, have a poor prognosis. It is important to detect ICC in its early stage to achieve better outcomes and better patient care. In this context, radiologists need to know the predisposing

✉ Kazuto Kozaka
k-kozaka@staff.kanazawa-u.ac.jp

[1] Department of Radiology, Kanazawa University Graduate School of Medical Sciences, 13-1 Takara-machi, Kanazawa 920-8640, Japan

[2] Department of Radiological Technology, School of Health Sciences, College of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Kanazawa, Japan

Table 1 Classification of cholangiocarcinoma

Classification of cholangiocarcinoma based on its anatomical location
Intrahepatic cholangiocarcinoma (ICC)
Perihilar cholangiocarcinoma
Distal cholangiocarcinoma
Classification of intrahepatic cholangiocarcinoma based on morphological appearance
Intraductal growth type of ICC (IG-ICC)
Periductal infiltrative type of ICC (PI-ICC)
Mass-forming type of ICC (MF-ICC)

conditions that can lead to the development of ICC. In this article, we discuss and illustrate the radiologic features of ICC with special attention to early-stage disease and predisposing conditions of ICC.

Precancerous ICC lesions and early ICC

Until now, and unlike in the case of HCC, there have been no worldwide accepted criteria or concepts for diagnosing early ICC [8, 9]. In this article, we discuss early detection of ICC, including both precancerous lesions and carcinomas in situ or minute invasive carcinomas [10]. The former include biliary intraepithelial neoplasm (BilIN), intraductal papillary neoplasm of the bile duct (IPN-B), and mucinous cystic neoplasm of the liver (MCN-L), according to the 4th edition of the WHO classification of tumors of the digestive system published in 2010 [1]. The latter includes early lesions of ICC defined in the TNM classification—T1: solitary and negative for vessel invasion (T1a, solitary tumor $\leq$ 5 cm; T1b, solitary tumor > 5 cm) [11], or Liver Cancer Study Group of Japan classification—T1: solitary tumor $\leq$ 2 cm and negative for both vessel and serosal invasion, based on its acceptable curability [12].

Precancerous ICC lesions

According to the WHO classification [1], low to intermediate epithelial atypia of BilIN, IPN-B, and MCN-L were first classified as precancerous and preinvasive tumors of ICC. Therefore, we describe these diseases as part one of "early detection of ICC" (Table 2).

Biliary intraepithelial neoplasm (BilIN)

Biliary intraepithelial neoplasm is a flat or micropapillary lesions histologically characterized by atypical epithelial cells and micropapillary projections into the biliary duct lumen; it can be classified as a low-grade dysplasia of biliary epithelium (BilIN-1), a high-grade dysplasia (BilIN-2), and a carcinoma in situ (BilIN-3), according to the degree of atypia [13, 14]. A BilIN is commonly found in the surgical specimen in which patients undergo surgical resection for hepatolithiasis [13] (Fig. 1). As a BilIN is a microscopic change of the biliary epithelium, conventional imaging modalities such as ultrasonography (US), CT, and MRI have limitations when used to evaluate this bile duct lesion. However, because BilIN is commonly associated with chronic biliary inflammation, radiologists should pay attention to inflammatory biliary lesions such as sclerosing cholangitis, whether there is a solid nodule or not. It has also been reported that intraductal biliary neoplasia was seen in liver cirrhosis and were accompanied with fibrotic changes [15]. In this report, peripheral enhancement with centrally hypoenhancement area was seen in early and delayed phase of dynamic CT, which corresponded to mixed inflammatory, fibrotic tissue and hepatic lobules in conjunction with intraductal biliary neoplasms. It can be noted that secondary inflammatory or fibrotic changes surrounding the lesions may help us identify them, however, it is quite difficult to differentiate them from non-neoplastic inflammatory lesions.

Table 2 Precursors for cholangiocarcinoma and risk factor of cholangiocarcinoma

Precursor of cholangiocarcinoma	
BilIN: biliary intraepithelial neoplasm	
IPN-B: intraductal papillary neoplasm of the bile duct	
MCN-L: mucinous cystic neoplasm of the liver	
Risk factors of cholangiocarcinoma	
Biliary infectious disease	Parasite infection (liver flukes, e.g. *Clonorchis sinensis*, *Opisthorchis viverrini*)
	Hepatolithiasis
	Primary sclerosing cholangitis
Congenital biliary disease	Anomalous pancreaticobiliary junction, choledochal cyst, Caroli disease
Environmental or occupational toxin	Thorotrast, dioxin, polyvinyl chloride
Hepatitis	Cirrhosis, chronic hepatitis (hepatitis B virus, hepatitis C virus)
Potential risk factors	Alcohol, smoking, diabetes, overweight, gallstone disease, inflammatory bowel disease

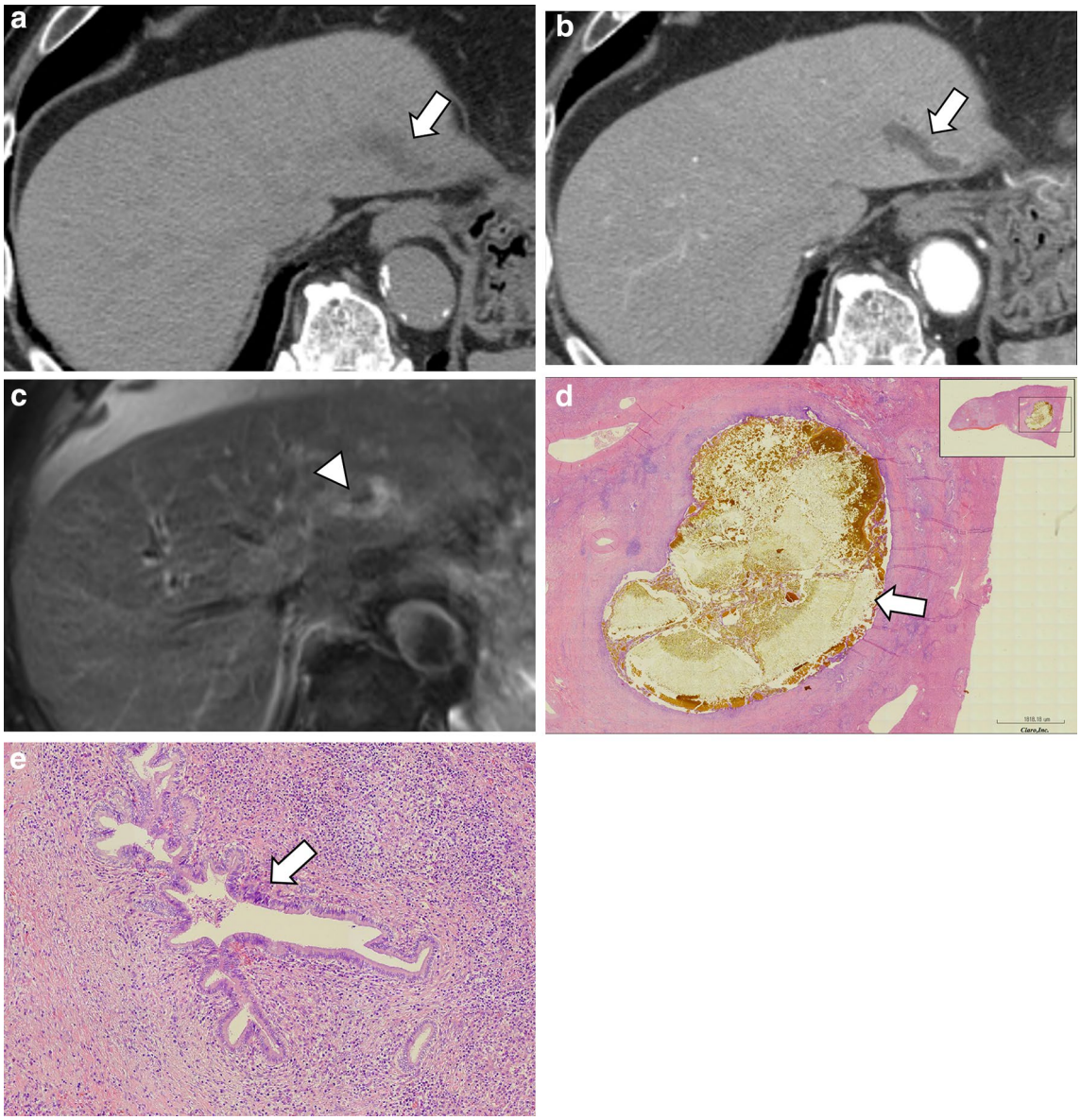

Fig. 1 A biliary intraepithelial neoplasm (BilIN) in a patient with an hepatic resection for hepatolithiasis. **a** A precontrast CT, **b** early phase of a dynamic contrast-enhanced CT, **c** T2-weighted MR image with fat saturation, **d** hematoxylin and eosin (H&E) staining of the lesion (low magnification), **e** H&E staining of a BilIN (high magnification). On CT, a dilated B2 is noted (**a** and **b**, arrow). There was no evidence of hepatolithiasis or of a biliary tumor. On a T2-weighed image, a nodular signal void was noted at the edge of the biliary dilatation (**c**, arrowhead). Radiological diagnosis of hepatolithiasis was made, and the patient was treated by lateral segmentectomy. Photomicrograph (H&E stain) shows an impacted cholesterol stone (**d**, arrow) with surrounding peribiliary inflammatory cell infiltration and dysplastic changes along the bile duct epithelium, which was diagnosed as a BilIN grade 1–2 (**e**, arrow)

Intraductal papillary neoplasms of the bile duct (IPN-B)

Intraductal papillary neoplasm of the bile duct (IPN-B) has recently been recognized as a new entity of biliary neoplasms, which present as grossly visible intraductal papillary lesions and include previous categories of biliary papillomas, papillomatosis and some of biliary cystadenoma without ovarian-like stroma [16]. Nakanuma et al. reported that a majority of intraductal growth type of ICC (IG-ICC) and biliary tract carcinomas with papillary growth could be regarded as belonging to the IPN-B lineage [17]. IPN-B is commonly considered as a preinvasive lesion in the dysplasia–carcinoma sequence, and if there is an invasive component, it would be referred to as an IPN-B with an associated invasive carcinoma [16, 17]. Although a vast majority of clinically detectable IPN-B is already malignant, being preinvasive or invasive variably, favorable prognosis can

be expected compared to other type of CC such as mass-forming and periductal infiltrating types [18].

Some recent studies have suggested that IPN-B is the biliary counterpart of intraductal papillary mucinous neoplasm (IPMN) of the pancreas based on their pathologic similarities. Although macroscopic mucin production is found in almost all IPMN of the pancreas, only about one-third of IPN-B contain visible mucus [19, 20], or if more strict IPN-B criteria like "papillary neoplasms confined to the epithelium without stromal invasion or those consisting of a neoplastic epithelium and thin fibrovascular stalks with an overall uniform papillary architecture throughout the tumour" applied, the ratio raises to more than two-third [21]. Pathologically, communication with the adjacent ductal system is commonly seen in both IPN-B and IPMN of the pancreas.

In the liver, morphologic patterns of IPN-B can be roughly classified into a cystic type which usually forms unilocular cystic mass and a non-cystic type which manifest intrahepatic bile duct lesion with or without duct ectasis (Fig. 2) [22]. Visualization of intraductal polypoid lesion depends on its size [23]. The duct ectatic type shows dilation of the affected bile duct often downstream and upstream, and even of the entire duct tree with or without a grossly visible intraductal mass (Figs. 2b, 3). The cystic type typically shows a large cystic lesion with the involved bile duct and various size of intracystic papillary masses (Fig. 4). Some cases appear as a cystic dilatation of the affected bile ducts without dilatation of the upstream and downstream ducts, which sometimes makes the correct diagnosis difficult [22, 24].

On dynamic CT/MRI, the affected bile ducts are variably dilated by the intraductal masses which are contrast-enhanced during the arterial dominant phase and show iso- to hypoattenuation/intensity relative to the surrounding bile duct wall in the portal venous and equilibrium phases [25, 26]. MRI has advantages in the detection and characterization of the IPN-B with its high soft tissue contrast. MR cholangiopancreatography (MRCP) is useful not only to detect intraductal lesions but to prove the communication between the dilated bile duct with the biliary tree, and to visualize the whole biliary tree without missing ducts, which is important in the evaluation of tumor extent and multiplicity [24, 27]. Diffusion-weighted MRI may improve the conspicuity of intraductal solid tumors with its higher contrast for solid tumors with substantial signal drop of surrounding normal tissue or fluid-filled bile duct and it may also be helpful in defining tumor invasiveness by periductal abnormal intensity [28]. A mucous plug may be seen as a floating nodular signal on an MRCP and sometimes mimics an intraductal mass.

The differential diagnosis of a non-cystic type of IPN-B includes HCC with biliary invasion, hepatolithiasis, and

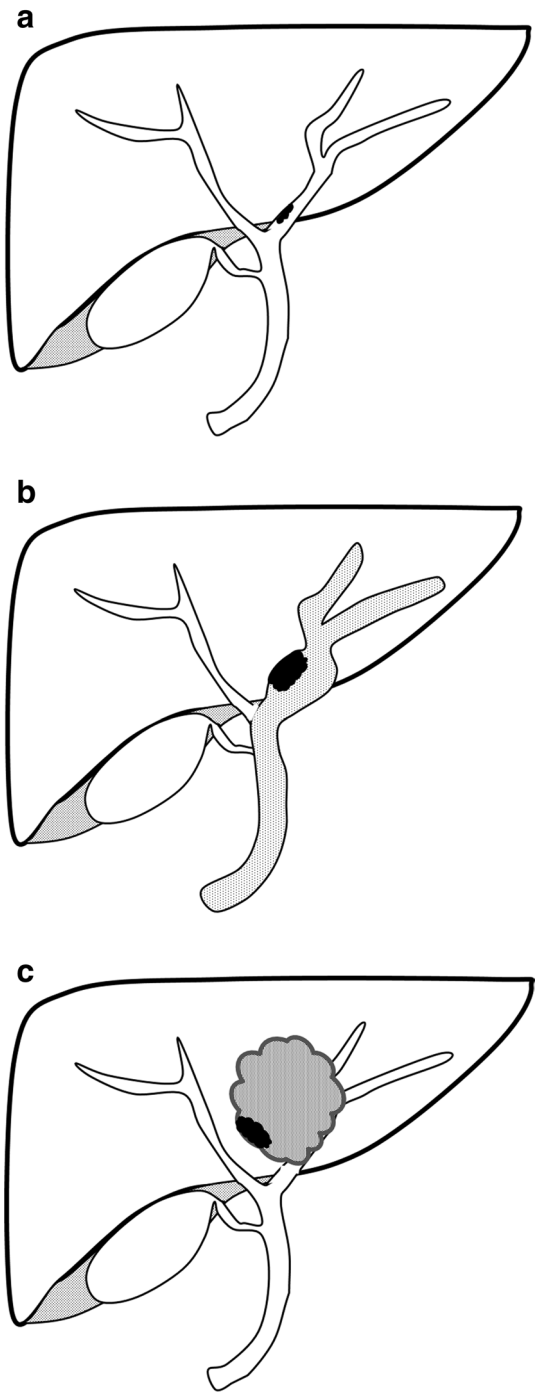

Fig. 2 Schematic of an intraductal papillary neoplasm of the bile duct (IPN-B) in the liver. An IPN-B can be classified on the basis of imaging as follows: cystic type as a cystic mass formation with or without identifiable communication with the bile duct on imaging (**a**) and non-cystic type (**b**, **c**). Non-cystic type can be further classified into non-duct ectatic type as intraductal masses without bile duct dilatation (**b**) and duct ectatic type as intraductal masses with bile duct dilatation (**c**). Note: the identification of an intraductal mass on imaging depends on its size

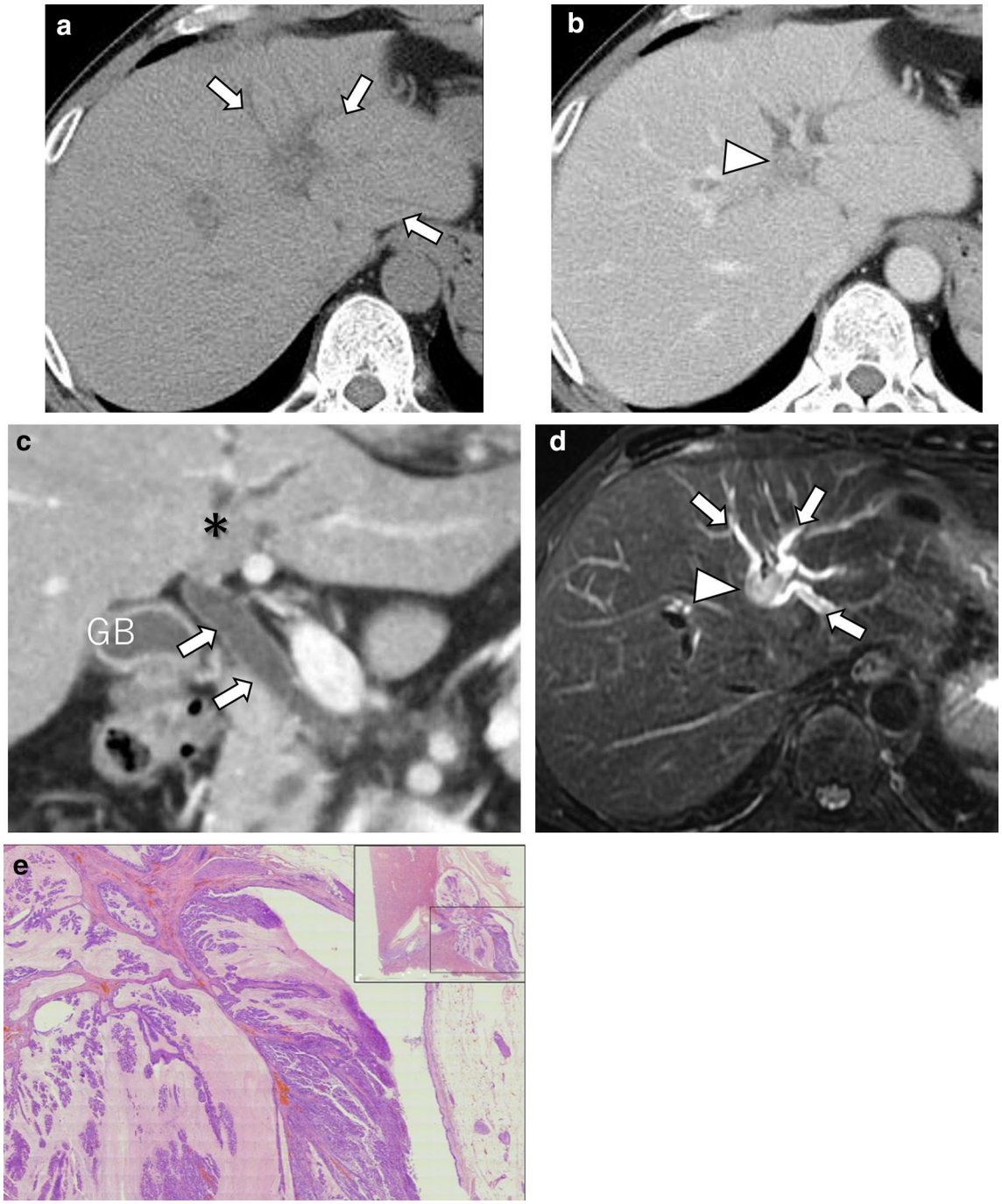

Fig. 3 Duct ectatic type of an intraductal papillary neoplasm of the bile duct (IPN-B). **a** A precontrast CT, **b** equilibrium phase of a dynamic contrast-enhanced CT, **c** coronal reconstruction image of the portal venous phase of a dynamic contrast-enhanced CT, **d** T2-weighted MR image with fat suppression, **e** H&E stain of the tumor (low magnification). On a precontrast CT, left intrahepatic bile duct dilatation was seen (**a**, arrows), but the cause of this was not clear. On a contrast-enhanced CT, a soft tissue density nodule was seen in the umbilical portion of the left portal area (**b**, arrowhead). On coronal image, dilatation of extrahepatic bile was also seen (**c**, arrows), probably because of an abundant production of mucin from the tumor (**c**, asterisk). A T2-weighted MR image clearly demonstrated the hyperintense intraductal tumor (**d**, arrowhead) and the dilatation of the upstream bile duct (**d**, arrow). A pathological specimen showed a papillary tumor with abundant mucin production (**e**). The tumor was a definite adenocarcinoma limited to the biliary epithelium (carcinoma in situ). *GB* gallbladder

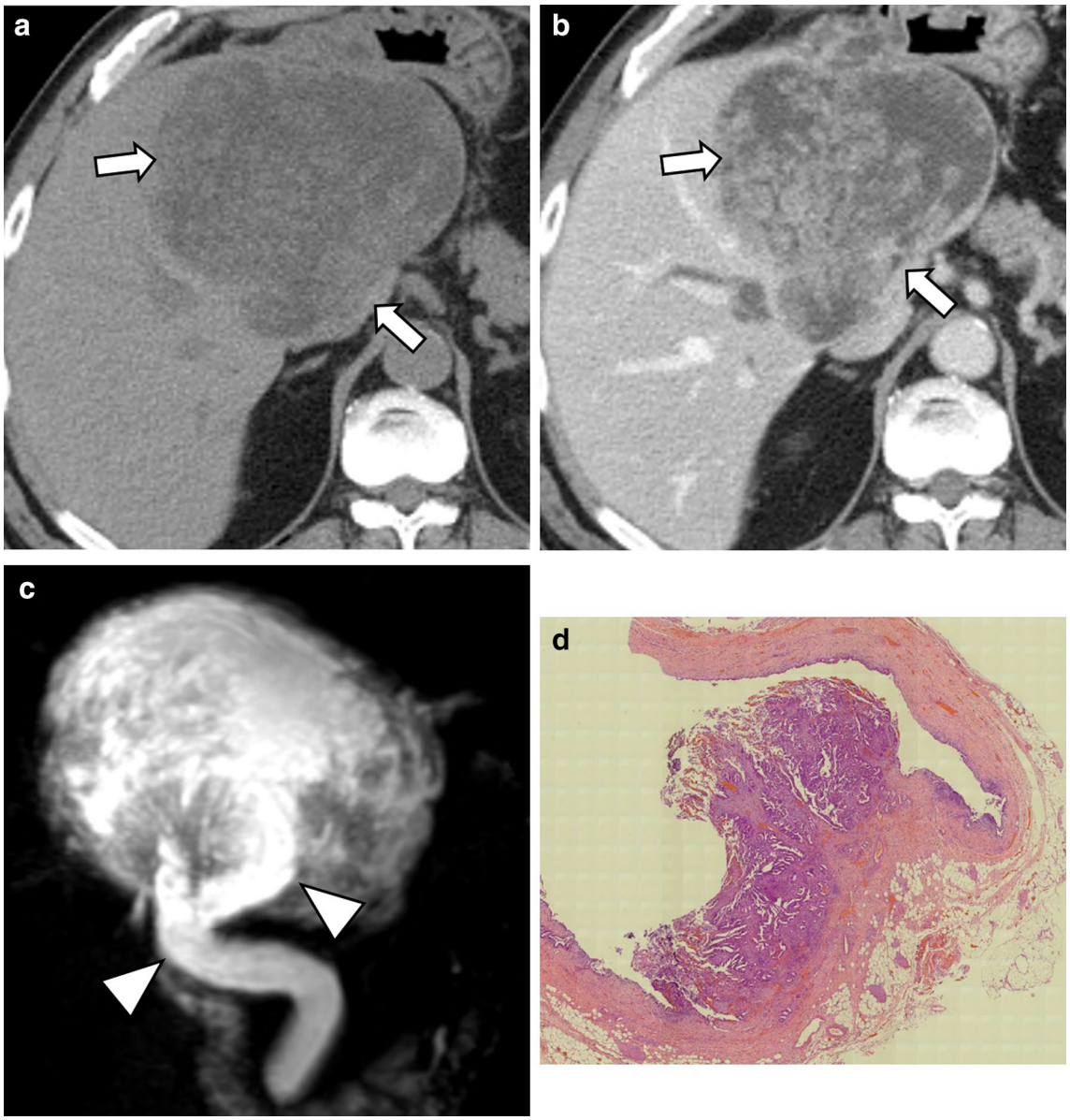

Fig. 4 A cystic type of intraductal papillary neoplasm of the bile duct (IPN-B). **a** A precontrast CT, **b** equilibrium phase of a dynamic contrast CT, **c** An MRCP image, **d** H&E stain of the tumor. On a precontrast CT, a large hepatic cystic mass with numerous polypoid lesions (**a**, arrows) was seen in left lobe of the liver. A contrast-enhanced CT demonstrated a weak enhancement of polypoid lesions (**b**, arrows). MRCP showed the connection between the tumor and the bile duct, and the dilatation of the downstream bile duct was also seen (**c**, arrowheads). A surgical specimen showed numerous polypoid tumors in the affected cystic bile duct. The content of the tumor was abundant mucosal fluid. The tumor was a definite adenocarcinoma limited to the biliary epithelium (carcinoma in situ)

metastasis to the biliary epithelium. Dynamic enhancement patterns are helpful in differentiating from HCC with biliary invasion. It is reported that a higher enhancement ratio of portal venous phase to precontrast images may favor a diagnosis of an IPN-B rather than HCC with biliary invasion [25]. The differentiation between IPN-B and metastasis to the biliary epithelium is sometimes difficult by cross-sectional images alone. Indeed, metastasis to the biliary epithelium is not rare entity [29], it is important for the correct diagnosis to obtain patients' information of previous history of malignancy or to screen whether there is another primary malignancy or not. Hepatolithiasis may also mimic an intraductal polypoid mass, especially when plain CT is not performed or when hepatolithiasis does not contain high calcium levels, the latter resulting in soft tissue density on plain CT. To identify hepatolithiasis with reduced calcium levels, a T1-weighted image is useful by showing it as a hyperintensity nodule [30]. On the other hand, the

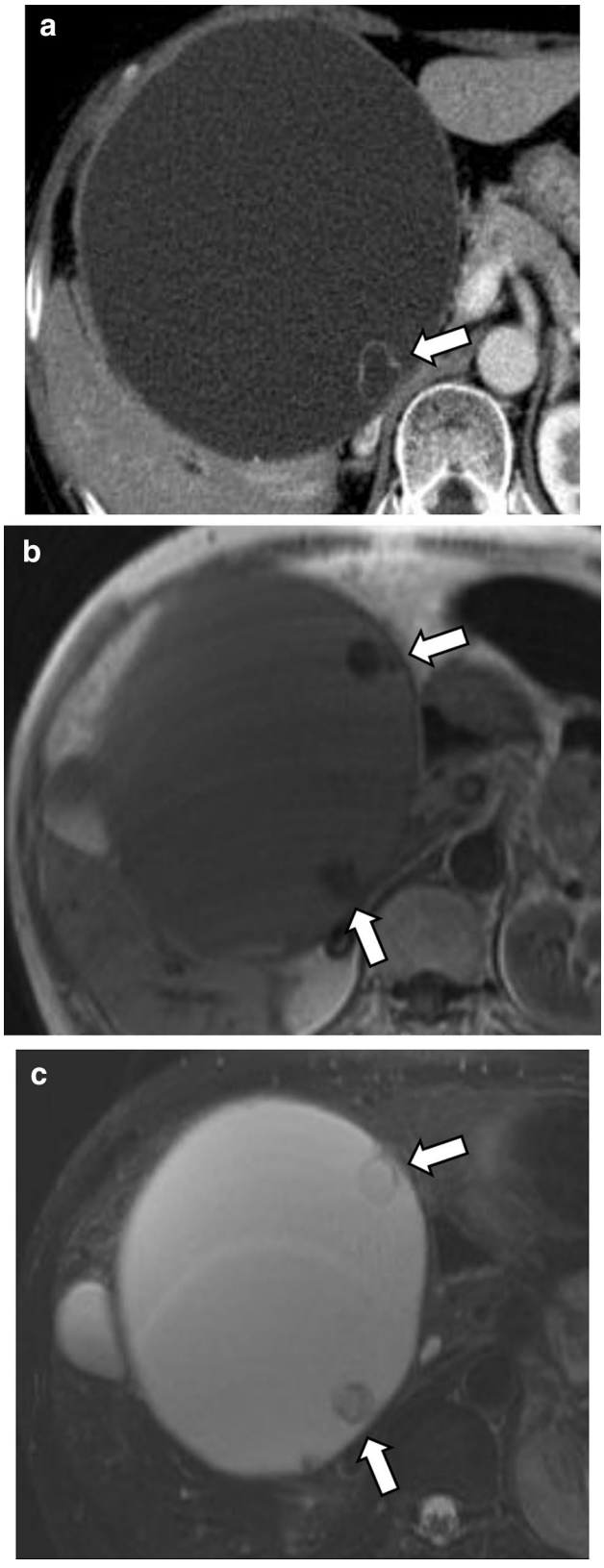

Fig. 5 A mucinous cystic neoplasm of the liver (MCN-L) in a female ▶ in her 40s. **a** A contrast-enhanced CT, **b** A T1-weighted MR image, **c** A T2-weighted MR image. A contrast-enhanced CT demonstrated a large cystic mass with a cyst-in-cyst appearance (**a**, arrow) in S4. On MR images, the cyst content showed a slightly hyposignal and hypersignal intensity on T1-weighted (**b**) and T2-weighted (**c**) MR images, respectively, which may mimic a hemorrhagic cyst. Small cysts inside the main cyst showed hyposignal and hypersignal intensity on T1-weighted (**b**, arrow) and T2-weighted (**c**, arrow) MR images. There was no evidence of a mural nodule on CT nor MRI. A surgical specimen was found to be an MCN-L with high-grade dysplasia (with no hepatic parenchymal invasion)

differential diagnosis of a cystic type of IPN-B includes a cystic metastasis, a simple cyst, a hemorrhagic cyst, and a mucinous cystic neoplasm of the liver (MCN-L). Though communication with bile ducts is one of the key features of IPN-B, some cystic IPN-B does not demonstrate such communication on neither cross-sectional images nor surgical explorations, probably given its origination from the peribiliary gland [22, 31].

Mucinous cystic neoplasm of the liver (MCN-L)

Mucinous cystic neoplasm of the liver (MCN-L) is described in the latest WHO classification of tumors of the digestive system and was previously referred to as cystadenomas and cystadenocarcinomas [16]. MCN-L is characterized by a cystic mass lined by dysplastic to neoplastic mucin-producing epithelium with ovarian-like subepithelial stroma and it occurs almost exclusively in women. As well as BilIN and IPN-B, the epithelium of MCN-L can be classified as low-, intermediate-, high-grade dysplasia on the basis of pathologic examination. An invasive carcinoma also can be seen in MCN-L and it is called MCN-L with an associated invasive carcinoma [16]. MCN-L is thought to be a liver counterpart of pancreatic MCN. Interestingly, most cases of MCN-P (> 95%) arise in the body and tail, whereas most cases of MCN-L arise in the left-sided biliary ductal system [32, 33], especially in S4, for unknown reasons. Since MCN-L has a malignant potential, complete resection is the therapy of choice for patients' better prognosis.

On imaging, cyst walls are typically thick [34] and may demonstrate delayed enhancement on dynamic CT/MRI. The internal septa and mural nodules may show variable enhancement, and a cyst-in-cyst appearance is often seen. The wall may contain discontinuous calcifications [33]. The cyst content shows a variable signal intensity on T1-weighted MR images and is usually hyperintense on T2-weighted MR images [34] (Fig. 5). Typically, there is no communication with the adjacent ductal system. Features suggestive of an associated invasive carcinoma include large size, irregular thickening of the cyst wall, and mural nodules and/or papillary excrescences projecting into the cyst [35]. The differential diagnosis of MCN-L includes cystic

IPN-B (as mentioned in the "IPN-B"), any solid tumors with cystic change or degeneration, hemorrhagic cysts, and even simple cysts [36]. When cyst-in-cyst appearance and/or stained glass appearance are demonstrated in a cystic mass in a middle-aged female patient, a MCN-L should be considered first [22].

Early intrahepatic cholangiocarcinoma

According to TNM classification, a Tis ICC is defined as a cancer limited in the mucosa and a T1 ICC is defined as a solitary lesion without vessel invasion. Among T1 ICC, a size of ≤5 cm is subclassified into a T1a and >5 cm is a T1b [11]. Conversely, using the Liver Cancer Study Group of Japan classification, a T1 ICC is defined as a solitary lesion without vessel invasion and a tumor size of <2 cm [12]. On cross-sectional images, what size of the tumor calls "small" has changed with the advance of imaging modalities. Although the concept of early HCC has been widely accepted [9], there is no confident concept of early ICC [37]. Thus, in this section, we discuss small ICC ≤3 cm.

Grossly, ICC can be classified into mass-forming (MF), periductal infiltrating (PI), and intraductal growth (IG) types according to the spread mode of the ICC [12, 38]. Among them, most common ICCs are of the MF, mixed MF and PI types. Although the pathogenesis of ICC is not clear, two possible pathways can be considered. One is the relationship with stem cells located in bile duct epithelium or the peribiliary gland, and the other is stem cells located in and around the peripheral portal areas such as bile ductules and the canal of Hering [39, 40]. ICC arising in the former may develop as BilIN or IPN-B. BilIN may progress to PI-ICC and as the tumor grows along the bile duct, it infiltrates into the periportal hepatic parenchyma. Eventually, these lesions fuse together to form a large mass or a mixed MF and a PI-ICC [41]. IPN-B may progress to invasive carcinoma, as discussed in the IPN-B section [31]. On the other hand, ICC arising in the latter may develop as intrahepatic cholangiocarcinoma of the mass-forming type (MF-ICC), possibly given the unique growth nature of cancer cells, that is replacing infiltrative growth [39, 42].

MF-ICC is the most common form of ICC [43]. Currently, dynamic CT and MRI are the primary imaging modalities enabling the detection and characterization of focal liver lesions as well as the staging of malignant tumors. On CT and MRI, typical MF-ICC is seen as a large tumor because ICC is often asymptomatic and such large tumors have been described as multilobulated hypovascular masses with peripheral rim enhancement and gradual centripetal contrast enhancement on dynamic studies (Fig. 6a). However, small (≤3 cm in diameter) MF-ICC of the liver show atypical enhancement patterns (arterial enhancing and/or washout in the portal venous phase) more frequently than large (>3 cm) MF-ICC, and such atypical enhancing MF-ICCs are often seen in the cirrhotic liver [44, 45] (Fig. 6b). In clinical practice, arterially enhancing MF-ICCs with washout could be misdiagnosed as HCCs, resulting in administering an inappropriate treatment such as trans-arterial chemoembolization (TACE), radiofrequency ablation (RFA), or percutaneous ethanol injection, which are frequently used for treating HCCs, though these might be palliative treatment options [46]. Thus, when a hepatic hypervascular lesion is seen particularly in cirrhotic liver, radiologists should keep in mind the possibility of an ICC (see "Cirrhosis"). Other differential diagnoses of atypical enhancing small MF-ICC may include hypervascular metastasis, combined hepatocellular cholangiocellular carcinoma, and benign lesions such as sclerosed hemangioma, FNH-like lesion, and pseudolymphoma [47–49].

PI-ICC is commonly seen in the perihilar region and the intrahepatic large duct [50–52]. On the other hand, as mentioned in MF-ICC paragraph, pure PI-ICC is rarely seen in the periphery of the liver, instead of mixed MF and PI-ICCs. Pathologically, PI-ICC arises from biliary epithelium and spread along biliary tract in conjunction with invading to peribiliary interstitial tissue with various degrees of inflammatory change [1, 53]. In cross-sectional imaging, affected bile duct wall shows irregular thickness or even nodular formation and secondary dilatation of peripheral bile duct is also commonly seen [53]. These image features of PI-ICC may overlap with benign stricture caused by primary or secondary sclerosing cholangitis [54, 55]. Although the diagnosis of PI-ICC in its early stages is challenging, the findings of progressive focal ductal enhancement as well as periductal soft tissues may be helpful to suggest a malignant stricture [56].

Intraductal growing ICC (IG-ICC) is the least common growth type (10% of all ICCs) and their CT/MRI findings share those of IPN-B, as described in the "IPN-B".

Risk factors of ICCs

There are several underlying factors that affect biliary carcinogenesis (Table 2) [46, 57, 58]. Although the mechanism of carcinogenesis of ICC is not well understood compared with HCCs, and although most cases of ICC have no definite associated etiology, it is well known that recurrent or chronic inflammatory diseases of the bile ducts are closely associated with an increased incidence of ICC [5]. In this section, we will discuss the important diseases that can lead to the development of ICC, such as chronic biliary or hepatic inflammation, primary sclerosing cholangitis (PSC), congenital biliary malformation, and other conditions.

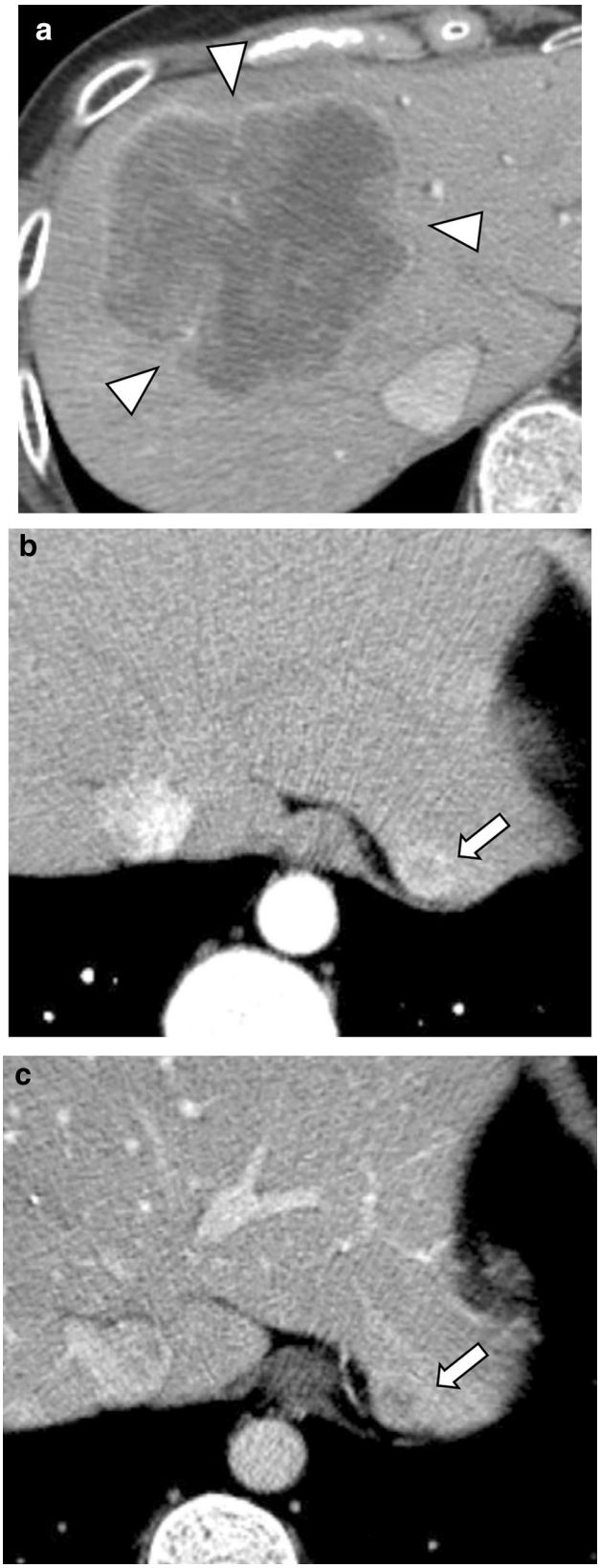

Fig. 6 Comparison between typical and atypical mass-forming type ▶ of intrahepatic cholangiocarcinomas (MF-ICCs). **a** A typical MF-ICC arising in a normal liver (no definite risk factor for ICC). A contrast-enhanced CT demonstrated a multilobulated hypovascular mass with peripheral rim enhancement in S8 (**a**, arrowhead). Upstream bile duct dilatation was also seen (not shown). **b**, **c** An atypical MF-ICC in a patient with cirrhosis. A dynamic contrast CT demonstrated a solid nodule in S2 with arterial enhancement (**b**, arrow) and wash out (**c**, arrow), which mimics an HCC

Hepatolithiasis

Hepatolithiasis is common in East Asian countries such as Taiwan, South Korea, China, Hong Kong, and others [59]. Although it is not common in Western countries, the disease is on the rise because of increased immigration from endemic areas [60]. It is noted that there is a risk that any conservative treatment for hepatolithiasis may allow an unrecognized CC to progress or phlogistic conditions predisposing to subsequent neoplastic degeneration to persist [61]. In fact, detection of concomitant hepatolithiasis-associated CC during treatment of hepatolithiasis was reported with an incidence rate of 5.3–12.9% [62].

About 80% of hepatolithiasis are composed of calcium bilirubinate and thought to be a result of bacterial infections in bile ducts, whereas 5–15% are mixed with variable amounts of cholesterol and calcium salts for the supersaturation of cholesterol and association of apolipoprotein A-1. For the detection of biliary stones, US is widely used because of its availability, lower cost, absence of radiation exposure, and ability to detect the lesion. But its diagnostic performance depends on the skill of the technician and the patient status. CT has a high degree of objectivity, but its ability to detect biliary stones highly depends on the amount of calcium in the stone. Conversely, MR imaging is most helpful for depicting hepatolithiasis as a high signal lesion on a T1-weighted image because of T1 shortening by bilirubin or trace metals contained in the lesion and a low signal on a T2-weighted image and MR cholangiopancreatography relative to adjacent bile juice [30]. It was reported that MRI and MRCP had higher sensitivity, specificity, and accuracy for detecting choledocholithiasis than US and CT [63].

Hepatolithiasis can evoke chronic inflammation of the bile duct, resulting in fibrosis of the bile duct wall, so called sclerosing cholangitis [64, 65] and cholangiocarcinoma. However, differentiation between focal sclerosing cholangitis arising in hepatolithiasis and early ICCs is challenging [50], and in fact, many ICCs are found incidentally during an operation for hepatolithiasis [66]. The atrophy of the hepatic lobe or segment suggests that such hepatolithiasis is a long-standing disease, and radiologists should take into account the potential for coexistence of a neoplastic lesion such as a BilIN, which is a microscopic lesion, or an early ICC (Fig. 1). Impacted hepatolithiasis itself may mimic an IPN-B

or an IG-ICC. The intraductal lesion showing a hyperechoic spot with an acoustic shadow on US, high attenuation on plain CT, or hyperintensity on a T1-weighted image are suggestive of hepatolithiasis rather than of an IPN-B or an IG-ICC [30].

Congenital biliary diseases

Congenital diseases of intrahepatic bile ducts include Caroli disease, autosomal recessive polycystic kidney disease (ARPKD), autosomal dominant polycystic kidney disease (ADPKD), Caroli syndrome, congenital hepatic fibrosis, and von Meyenburg complexes [67]. These are a heterogeneous group of genetic disorders, of which segmental dilatations of the intrahepatic bile ducts and associated fibrosis can be interpreted as sequelae of persistence and/or aberrant remodeling of the embryonal ductal plate (ductal plate malformation) [67]. Among them, Caroli disease is characterized by grossly visible saccular or cystic dilatation of the intrahepatic bile ducts and often simultaneously seen multiple intrahepatic calculi [34]; it is one of the well-known risk factors of CC, including papillary tumor, because it causes chronic bile stasis, recurrent cholangitis, and chronic inflammation [68, 69] (Fig. 7a, b). Even though von Meyenburg complexes (VMCs) are now thought of as biliary hamartomatous lesions, some reports indicated that it was a precancerous lesion because some CCs show VMC features or coexist with VMC [70]. In clinical practice, it is difficult to predict early progression of CC from VMC. Lee et al. raised an alarm that as a VMC is potentially precancerous lesions, they require careful follow-up in terms of any size increase, and biopsies are essential to determine any proliferative epithelial changes including dysplasia and malignant transformation [70], yet the incidence of ICC arising in VMC appears to be quite rare.

Congenital biliary disease of extrahepatic ducts includes choledochal cystic lesions and biliary atresia, and both often show intrahepatic biliary abnormalities. A congenital choledochal cyst can develop into a CC that is not only restricted to the extrahepatic bile duct or gallbladder but also to the intrahepatic bile duct with a lifetime risk of 10–15% [3]. Since CC can develop in about 1% of patients including those who underwent surgery (Fig. 7c) [71], periodic follow-up even after excision of the choledochal cyst for early detection of a CC is mandatory.

Biliary atresia is severe in neonatal liver disease, characterized by extrahepatic ductopenia, intrahepatic bile duct paucity, and progressive obliterative cholangiopathy [67]. The Kasai procedure is recommended for an infant with biliary atresia within 60 days. Even if the Kasai procedure is successful, recurrent cholangitis followed by progressive jaundice and biliary cirrhosis develops early in life. Malignant epithelial tumors such as HCC, CC, and hepatoblastoma

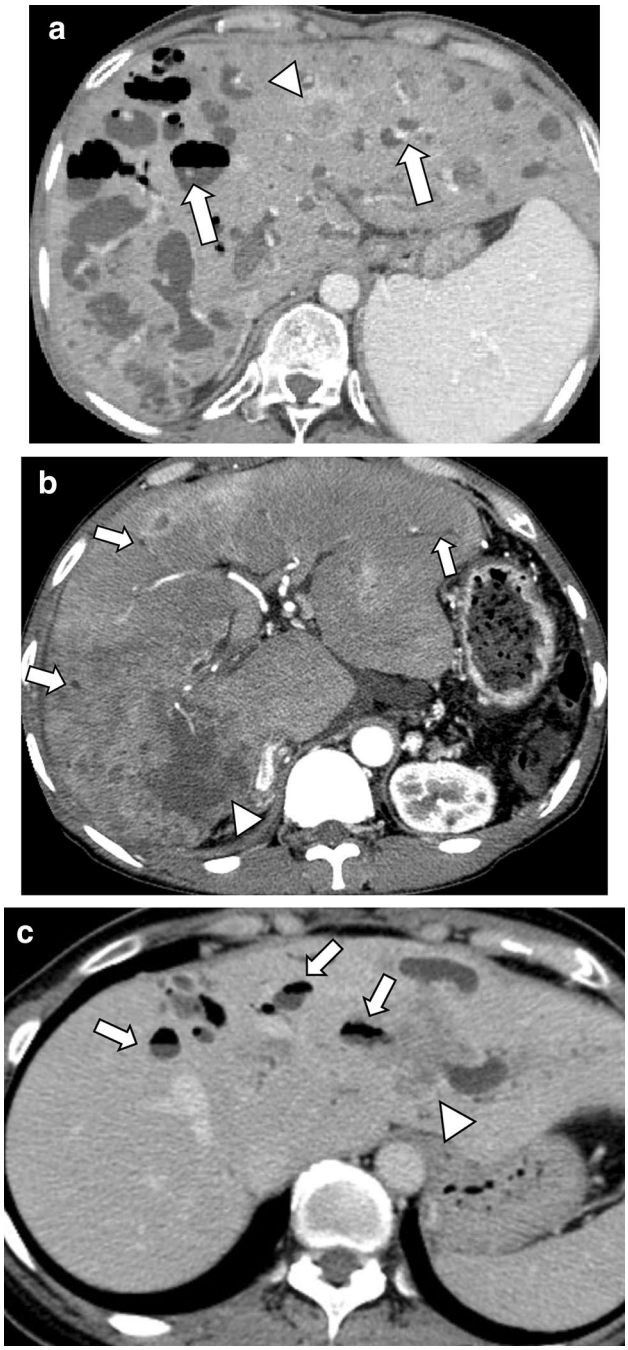

Fig. 7 An intrahepatic cholangiocarcinoma (ICC) arising in various congenital biliary anomalies. **a** An ICC arising in Caroli disease, proved by autopsy. On the portal venous phase of a dynamic contrast-enhanced CT, distorted dilated bile ducts can be seen as noted (arrows). Some distorted bile ducts contained air, which occurred because of repeated irrigation of the bile duct for the treatment of cholangitis with hepatolithiasis. Autopsy was performed and it revealed an ICC on S3 (arrowed) with impacted hepatolithiasis. **b** An ICC arising in a congenital hepatic fibrosis, proved by biopsy. On the hepatic arterial phase of a dynamic contrast-enhanced CT, a hypoattenuated tumor with an irregular border can be seen in S7 (arrowhead). The background liver shows hepatomegaly with an irregularly dilated intrahepatic duct (arrows). **c** An ICC developed 20 years after surgical removal of a choledochal cyst, proved by pathology of the surgical specimen. On equilibrium phase of a dynamic contrast-enhanced CT, a multiloculated hypoattenuated tumor was seen in the lateral segment (arrowhead). An intrahepatic bile duct dilatation that contained air was also seen (arrows)

of hepatobiliary origin rarely occur in biliary cirrhosis associated with biliary atresia [72].

Primary sclerosing cholangitis (PSC)

PSC is a chronic disease with progressive fibrosing inflammatory destruction of intrahepatic and extrahepatic bile ducts and cholestasis [65], which is often associated with inflammatory bowel disease. The incidence of PSC is low in Asia and is relatively higher in Western countries; the prevalence ranges from 0 to 16.2 per 10,000 [65]. PSC is typically progressive, with cirrhosis developing in the majority of patients within 10–20 years (so called biliary cirrhosis), and patients with late-stage PSC are considered to be good candidates for liver transplantation [65]. Additionally, patients with this disease are at increased risk of certain cancers that are a substantial cause of morbidity and mortality [55, 65, 73]. Although CC can develop not only in extrahepatic and perihilar bile ducts but also in intrahepatic bile ducts, one recent study revealed that ICCs arising in PSC patients are associated with the intrahepatic large duct [43], which has similar morphological characteristics and cell marker expression to the extrahepatic bile duct [6]. The frequency of CC anywhere is higher than the 0.5–1.5% risk per year [40, 46]. Various population studies demonstrate that there is a variable risk of developing CC, with a subset of patients developing CC within the first year of diagnosis of PSC (one-third and up to one half of patients who develop CC) [46]. Thus, careful checkup for CC is needed, especially in the first 2 years from when the diagnosis of PSC is made.

For the diagnosis of PSC, MRCP shows sufficient diagnostic performance by demonstrating characteristic findings of PSC: multifocal strictures of the biliary tree alternating with unaffected normal caliber ducts resulting in a beaded appearance [74]. However, MRCP alone may be imprecise in differentiating a malignant tumor from benign strictures in PSC because MRCP can demonstrate only luminal changes, and the MRCP finding overlaps between the findings related to PSC and CC [73]. Although most of CC in PSC are perihilar cholangiocarcinoma, ICC also can be seen with various morphologic appearances. Contrast-enhanced CT and MRI can demonstrate ICC as focal bile duct wall thickening with hyperenhancement in the arterial or portal venous phase, intraductal polypoid masses with/without biliary dilatation in the periphery of the tumor, or intrahepatic masses with periphery rim-like enhancing in the arterial phase and central gradual enhancement in the portal to delayed phase [75] (Fig. 8). Irregular ductal narrowing with shouldered margins, marked or rapidly progressed biliary dilatation, and atrophy of the affected hepatic lobe/segment are suggestive imaging findings of the development of CC in PSC [76, 77]. However, when active inflammation is seen in patients with PSC, irregular peribiliary or hepatic enhancement may be present [78] and may mask the findings of the CC (Fig. 8). Some studies have reported that ^{18}F-FDG PET may be useful for detecting CC in patients with PSC [79, 80].

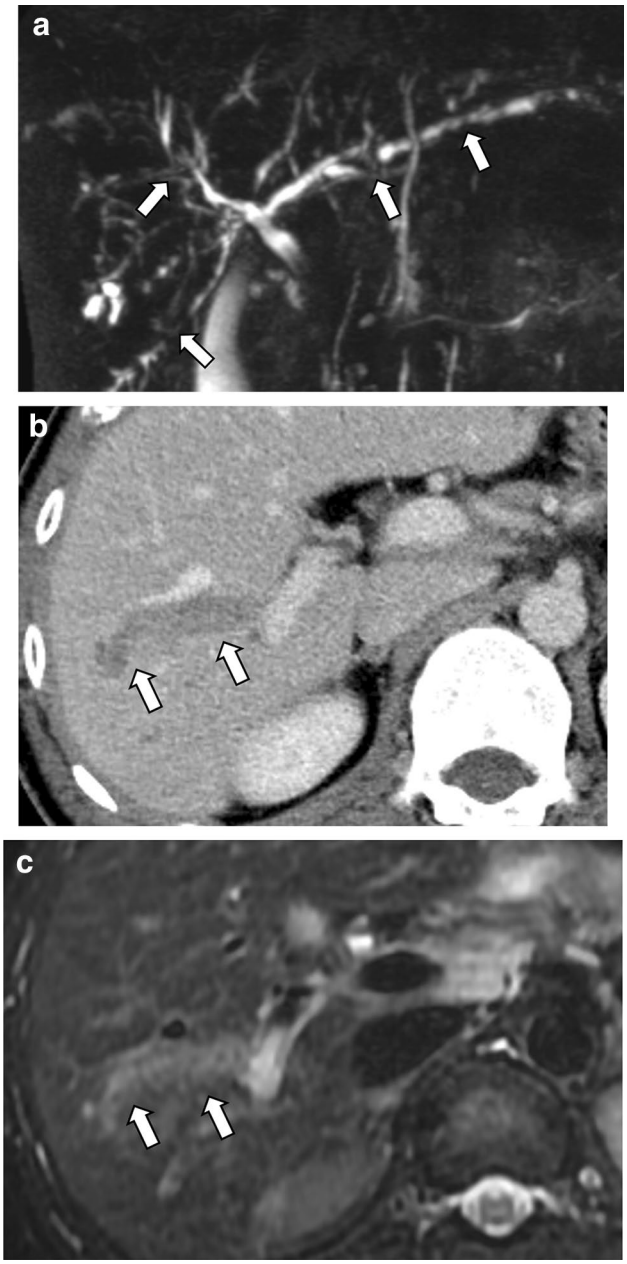

Fig. 8 An intraductal growth type of an intrahepatic cholangiocarcinoma in a male patient in his 40s with a primary sclerosing cholangitis (PSC) diagnosed 2 years ago. **a** A MR cholangiopancreatography (MRCP), **b** portal venous phase of a dynamic contrast-enhanced CT, **c** a T2-weighted MR image with fat saturation. A MRCP showed multifocal biliary strictures alternating with areas of biliary dilation (**a**, arrows). A contrast-enhanced CT image showed a soft tissue tumor in the B6 bile duct with a mold shape (**b**, arrows). An axial T2-weighted MR image showed the tumor as a slightly hypersignal intense lesion inside the duct (arrows). The tumor was an intraductal papillary carcinoma with minute hepatic parenchymal invasion, as determined pathologically

Parasitic infections

Among several risk factors of CC, infection with liver flukes (e.g., *O. viverini* and *C. sinensis*) is one of the most common causes of CC in endemic areas such as the Far East and Southeast Asia [81]. Even in non-endemic areas, these infections are increasing especially in the area of poor sanitation, overpopulation, or the area where the active turnover of people or food. Dietary or endogenous nitrosamine compounds associated with parasitic infections also play an important role as cofactors in carcinogenesis, probably because of the carcinogenic effect of nitrosamine compounds on the proliferation of epithelial cells of the bile duct [82]. Upon microscopic examination, a degenerated larva may be seen within the dilated duct with marked periductal fibrosis and inflammation [66]. Innumerable eggs can also be present in the ductal lumen.

On imaging, the association of ICC with clonorchiasis may be characterized by prominent ductal dilatation, not only in the peritumoral area but also in remote areas of the liver (Fig. 9). Most clonorchiasis-related ICC show intrahepatic mass at the time of clinical diagnosis, and an ICC with prominent mucin secretion is another representative manifestation [66, 83, 84].

Cirrhosis

Cirrhosis has been recognized as an important risk factor of not only HCCs but of ICCs as well [46, 85, 86]. In a cohort study of over 11,000 patients with cirrhosis followed up over 6 years, a tenfold excess risk of ICC was found compared with the general population [86]. In addition, the MF-type ICC at the periphery of the liver is known to have a higher association with cirrhosis or HBV and HCV than other types of ICCs [46, 87, 88]. A Japanese prospective controlled study found that the risk of ICCs in HCV-related cirrhosis was 3.5% after 10 years, 1000 times greater than that in the general population, and there is a reported adjusted odds ratio of 22.9 for cirrhosis, 5.1 for HCV infection, and 4.8 for HBV infection [89]. There is a significantly increasing number of small ICC during follow-up and screening for HCC in cirrhotic patients.

On imaging, a MF-ICC arising in cirrhosis tends to show an atypical enhancement pattern including early enhancement of the nodule in dynamic CT and MRI, which mimic HCCs in clinical practice, especially those smaller than 2 cm in diameter [44, 45] (Figs. 6b,c, 10). Although the frequency is not high, washout in the portal venous phase is sometimes seen in MF-ICC arising in a cirrhotic liver. Peripheral bile duct dilatation and delayed enhancement of the nodule with no evidence of a fibrous capsule of the nodule are key images features of ICC rather than of HCC [45].

Chemicals

Various chemicals have been linked to CC. The banned carcinogenic contrast agent, thorium dioxide (Thorotrast) has been strongly associated with CC because of high accumulation to the liver [90], although this was used more than 50 years ago as a contrast medium for radiography and is not in use nowadays [91]. It has resulted in various neoplasms including CC, by exposure of the body to alpha particles. Epidemiological associations have been made to industrial toxins such as dioxins and nitrosamines [92]. CCs have been reported in printing company's workers exposed to chlorinated organic solvents, and they have consequently been classified as an occupational disease (occupational cholangiocarcinoma) by the Japanese Ministry of Health, Labour and Welfare [93]. It is worth noting that MRI/MRCP findings of CC developing in printing company workers sometimes mimic those of PSC [94].

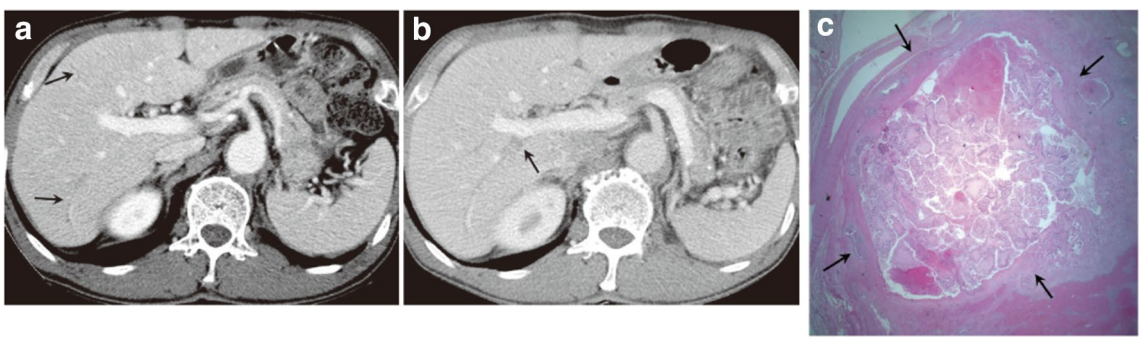

Fig. 9 An intraductal papillary adenocarcinoma that developed during 3 years of follow-up in a patient with clonorchiasis. **a** A CT shows a mild dilatation of an intrahepatic duct (arrows). **b** A CT image 3 year later shows a focal dilatation of a segmental bile duct, which is filled with a small, soft tissue mass (arrow). **c** A microphotograph shows a focally invasive tubular adenocarcinoma that developed from a papillary adenoma within the lumen of a bile duct (arrows). The intraductal papillary neoplasm is sizable and it is visible macroscopically and radiologically (scanning power view, ×1). Cited from [81] (permission obtained)

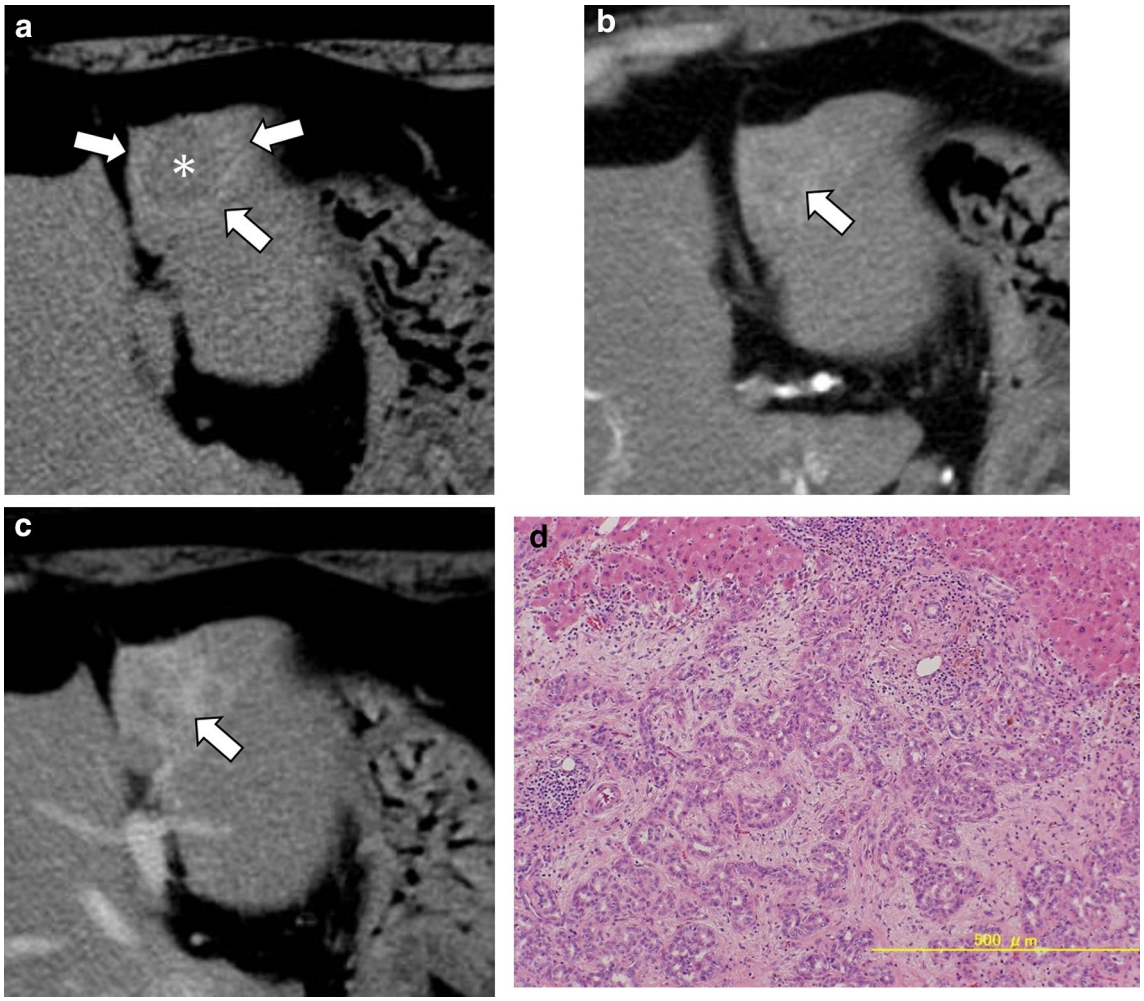

Fig. 10 A mass-forming-type intrahepatic cholangiocarcinoma with atypical imaging features arising in a male patient in his 70s with alcoholic liver cirrhosis. **a** A precontrast CT, **b** hepatic arterial phase, **c** equilibrium phase of a dynamic contrast-enhanced CT, **d** H&E stain of the tumor. A hypoattenuated nodule was seen in S3 on a non-contrast CT (**a**, asterisk). A perinodular hyperattenuation area was noted, probably because of focal fat sparing in the diffuse fatty liver (**a**, arrows). The nodule showed irregular early enhancement (**b**, arrow), and delayed enhancement was seen in the equilibrium phase. The pathological specimen showed small tubular carcinoma cells that were seen in the abundant fibrous tissue (**d**)

Miscellaneous

Benign tumors of the bile ducts are rare. Among them, bile duct adenoma (BDA) is the most common benign neoplasm of the bile duct; it is characterized by the proliferation of bile duct epithelium and can be divided into intrahepatic and extrahepatic BDAs, according to their location [95]. Pathologically, an intrahepatic BDA would be considered as a peribiliary gland hamartoma because both share common antigens [96]. It is usually a solitary, < 10 mm in diameter, and peripherally located lesion of the liver that appears as an arterially enhancing mass that should be differentiated from other hypervascular hepatic tumors [97, 98]. Although BDA is a benign lesion, there are some ICC cases coexisting with BDAs [58]. Preoperative diagnosis of a BDA itself is difficult due to its small size, subcapsular location and overlapping imaging features of ICC or metastases [99]. Thus, radiologic detection of malignant foci or prediction of the possibility of malignant transformation of a BDA seems quite challenging.

Solitary bile duct cyst (hepatic cyst) is the most common benign cystic lesion of the liver lined by columnar or cuboidal bile duct epithelium. There are sporadic reports of an adenocarcinoma arising in a solitary hepatic cyst, where part of bile duct epithelium shows cellular atypia or papillary projection [100, 101]. The imaging features of adenocarcinoma arising in simple hepatic cyst may be similar to those of MCN-L although the pathologic features are totally different as mentioned in "MCN-L".

Conclusion

Current evidence suggests that the prevalence of CC is increasing worldwide. Diagnosis of "early-stage" ICC and their complete resection is essential for a complete cure. Diagnosis of early-stage ICC or precancerous lesions of ICC is challenging, but it is important for radiologists to be familiar with pathological conditions at high risk of developing ICC and, therefore, the need for careful interpretation of imaging results for such diseases. Although peripheral bile duct dilatation is an important key feature of ICCs, this finding is also seen in inflammatory biliary disease. Furthermore, ICC may be hidden in chronic inflammatory diseases. When abnormal density, signal intensity, or enhancement around the biliary tract is seen on cross-sectional images, radiologists should not immediately diagnose it as focal cholangitis, but plan further examinations such as blush cytology and endoscopic biopsy or suggest careful follow-up using imaging to exclude an ICC.

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