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Review

Primary malignant tumours in the non-cirrhotic liver

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ABSTRACT

Intrahepatic chlangiocarcinomas (CCs), the second most common primary malignant liver tumours, usually occur in non-cirrhotic liver, and can be classified into three types based on gross morphology: mass-forming; periductal infiltrating; and intraductal growing. Among them, mass-forming intrahepatic CCs are the most common type and characterized by homogeneous mass with an irregular but well-defined margin with peripheral enhancement on late arterial phase and delayed enhancement in central portion of tumours corresponding to the fibrous stroma. Several imaging features such as enhancement pattern and degree of diffusion restriction have been suggested as prognostic markers for mass-forming CCs. Hepatocellular carcinomas (HCCs) are the most common primary malignant liver tumors, and usually arise from the cirrhotic liver. However, approximately 20% of HCCs involve the non-cirrhotic liver (hereafter, non-cirrhotic HCC), and non-cirrhotic HCCs are often detected at an advanced stage due to the lack of surveillance for patients with non-cirrhotic liver. Other primary malignant liver tumours other than CCs and HCCs including angiosarcoma, undifferentiated embryonal sarcoma are quite rare, and imaging diagnosis is often difficult. This review offers a brief overview of epidemiology, risk factors and imaging features of primary malignant tumours in non-cirrhotic liver. Understanding of radiologic appearance and predisposing clinical features as well as differentials of primary malignant tumour in non-cirrhotic liver can be helpful for radiologists to adequately assess these tumours, and subsequently to make optimal management plan.

1. Introduction

Primary liver cancer is the sixth most common malignant tumour with 5.7% of the overall incidence, and the third leading cause of cancer-related death worldwide indicating a very poor prognosis [1]. Among the various primary liver cancers, hepatocellular carcinoma (HCC) is the most common primary malignant tumours typically originated from the cirrhotic liver through the multistep process of hepatocarcinogenesis, although as many as 20% of HCCs can be developed in a non-cirrhotic liver [2,3]. In contrast to the HCCs, cholangiocarcinomas (CCs) which are the second most common primary liver cancer accounting for up to 15% of the cases [4,5] are usually developed in non-cirrhotic liver. Primary liver cancer other than HCCs and CCs including angiosarcoma, primary hepatic neuroendocrine tumor, lymphoma and undifferentiated embryonal sarcoma are quite rare, and also usually seen in the non-cirrhotic liver. With the widespread use of surveillance program of US for HCCs in patients with cirrhosis, typically HCCs, are frequently small at detection. However, Therefore, primary liver cancers in the non-cirrhotic liver are often detected at an advanced stage and are more likely to cause symptoms such as abdominal pain, distension, weight loss, anorexia, fatigue, and malaise [6,7]. Occasionally, these tumours can cause abnormal liver function test results such as jaundice.

For optimal management plan for patients with primary liver cancer in the non-cirrhotic liver, proper diagnosis and staging are of crucial importance. For example, surgical resection is the only curative treatment method with long-term survival for patients with CCs. Primary hepatic lymphoma should be treated with systemic chemotherapy. The prognosis of hepatic angiosarcoma is grave, and median survival after diagnosis has been known to be only several months. To achieve an exact diagnosis of primary liver cancers in the non-cirrhotic liver and subsequently to decide optimal management plan, understanding of imaging findings and clinical features are important as imaging studies including computed tomography (CT) or magnetic resonance (MR) imaging are usually done for the evaluation and diagnosis of a hepatic mass in the non-cirrhotic liver. In this report, we review the various imaging findings and clinical feature of primary liver cancers in the non-cirrhotic liver with the representative figures. Understanding of its

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appearance and predisposing clinical features can be helpful for radiologists to assess these tumours correctly.

2. Cholangiocarcinoma (CC)

CCs are malignant tumours arising from varying locations within the biliary tract showing cholangiocyte differentiation. Most CCs are adenocarcinoma with various differentiation, and abundant fibrous stroma is often accompanied[8]. CCs can be classified into three categories according to the anatomical location: intrahepatic CCs is defined as a CC located proximally to the second confluence of bile ducts within liver; perihilar CCs is located to the area between the second confluence of bile ducts and the insertion of the cystic duct into the common bile duct; and distal CCs is confined to the area between the origin of the cystic duct and ampulla of Vater. As perihilar CCs and distal CCs can be considered as bile duct origin tumour, we focused on intrahepatic CCs in this report. Intrahepatic CCs account for 10-20% of all primary hepatic tumours, and can be classified into three types based on the gross morphologic features: mass-forming, periductal infiltrating, and intraductal growing. Among these three types, mass-forming CCs are the most common type of intrahepatic CCs. Each type of CC has its own characteristic imaging findings. We discuss intrahepatic CCs in terms of the epidemiology, risk factors, imaging findings and prognostic implications.

2.1. Epidemiology and risk factors

CCs is the second most common primary malignant liver tumours. The prevalence of CCs varies markedly from one geographic region to another, and the highest prevalence was seen in Southeast Asia including Thailand [9–11]. Even though there has been a misclassification issue in the ambiguous classification of hilar CCs, the incidence of intrahepatic CCs seems to be increasing in many western countries. Most of the intrahepatic CCs arise de novo and sporadic, and there are no identifiable risk factors in many of cases. However, several established risk factors for CCs have been reported in several particular populations, and all of the risk factors share the common feature of chronic inflammation on the biliary tree [11]. The established risk factors for CCs also vary among the different geographic regions as the prevalence is. In Southeast Asia including Thailand where shows highest prevalence of CCs, infection with liver flukes (e.g., Opisthorchis viverrini and Clonorchis Sinensis) are common causes of CCs [12,13]. Hepatolithiasis is another common risk factor in parts of Asia, especially Japan, Taiwan, China, and Korea [8,9,11], and up to 7% of patients with hepatolithiasis eventually develop intrahepatic CCs. The mean time interval between the diagnosis of hepatolithiasis and the development of CCs is about 8 years, and tumors can appear even after complete stone removal [14]. On the contrary, in the West, primary sclerosing cholangitis (PSC) is the most common risk factor for CCs. The annual risk of developing CCs in patients with PSC has ranged from 0.5% to 1.5%, with a lifetime prevalence of 5%-10% [15], and CCs are detected within 2 years after the diagnosis of PSC in most of these patients. The duration or severity of PSC or inflammatory bowel disease is not seemed to be associated with the development of CCs [8].

Recently, liver cirrhosis and chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection have been reported as potential risk factors for developing intrahepatic CCs [16–19], and these risk factors are further supported by the newly developed concept of cancer stem cells and hepatic progenitor cells in primary liver cancers [20]. CCs detected in cirrhosis, or chronic HBV/HCV infection are frequently small probably due to the surveillance program for these patients and may manifest as small hypervascular tumors which can mimic HCC [21,22]. Choledochal cyst is a risk factor for developing either extrahepatic or intrahepatic CCs with a lifetime risk of 10%-15% [11,23]. According to the results of recent studies, inflammatory bowel disease independent of PSC, alcohol consumption, smoking, fatty liver disease and diabetes may increase the risk of development of CCs [23–25].

2.2. Imaging features of intrahepatic CCs

2.2.1. Mass-forming type CCs

Mass-forming type CCs, which are the most common type of intrahepatic CCs, show typical characteristic feature of homogeneous mass with an irregular but well-defined margin on imaging studies[26]. Dilation of biliary trees distal to the tumours is frequently seen, and vascular encasement by the tumour is also a common finding. However, in contrast to the HCCs, macroscopic portal and/or hepatic vein invasion and subsequent tumour thrombus formation are rare. On ultrasound, mass-forming type CCs appear as a homogeneous mass with an irregular border but well-defined margin [11]. The echogenicity of mass depends on the tumour size, and tumours less than 3 cm are hypo- or isoechoic whereas tumours greater than 3 cm usually show hyperechogenicity [27]. A peripheral hypoechoic rim which consists of compressed liver parenchyma or proliferating tumour cells can be seen in approximately 35% cases of mass-forming CCs [28].

On unenhanced CT scan, mass-forming type CCs typically appear as homogeneous hypodense mass compared to the adjacent normal liver parenchyma. When tumours arise from the preexisting hepatolithiasis, radio-dense intrahepatic duct stones with ductal dilatation and obliteration of portal vein accompanied by atrophic changes of the involved segment are frequently seen, and unenhanced CT image can play a major role to differentiate enhancing tumours from preexisting stones. After the administration of contrast media, mass-forming type CCs usually show irregular peripheral enhancement on late arterial phase images. On delayed phase which usually obtained 3–15 minutes after contrast injection, hyperenhancement in the central portion of the tumours can be seen in many of cases [22,29,30] (Fig. 1). However, up to 30% of mass-forming type CCs can show atypical enhancement pattern including arterial hyper-enhancement, and chronic liver disease or cirrhosis in background liver is more frequently found in patients with atypically enhancing mass-forming CCs [22]. Retraction of liver capsule, the presence of satellite nodules, and vascular encasement without formation of tumour thrombus are another characteristic findings of mass-forming CCs [11].

On gross specimen, mass-forming CCs appear as a homogeneous sclerotic mass with an irregular lobulated margin. Intratumoural hemorrhage or central necrosis is usually absent. On histologic analysis, the viable tumour cells are typically located at the periphery of the tumour which corresponds peripheral enhancement of the tumour on the late arterial phase of contrast-enhanced CT or MR [22,31]. The central portion of tumour consists of a variable degree of fibrosis and/or coagulative necrosis with scanty scattered viable tumour cells. It has been well known that degree of tumour central portion enhancement on the delayed phase is closely associated with the amount of interstitial space in the fibrous stroma [32].

Similar imaging features can also be seen on MR imaging (Fig. 1). The mass-forming CCs usually show high signal intensity on T2-weighted image and low signal intensity on T1-weighted image. Diffusion restriction is frequently seen on the peripheral portion of the tumour. Recently, liver-specific contrast agent such as gadoxetic acid has been increasingly used for liver imaging as hepatobiliary phase (HBP) provided by this kind of contrast can improve the detection and characterization of focal liver lesions. On HBP image, mass-forming type CCs typically shows low signal intensity due to the lack of functioning hepatocyte within the tumour [26,31]. However, a mild degree of contrast enhancement in the central portion of the tumour can be observed in hepatobiliary phase images, and this central enhancement can be explained by the contrast retention in the central fibrous stroma of the tumour [31]. Regarding the use of gadoxetic acid enhanced MR for the evaluation of mass-forming CCs, Kang et al. reported that HBP images show increased lesion conspicuity of mass-forming CCs compared to dynamic sequences, and better delineation of daughter nodules