

Retrospective Study

Liver metastasis from hepatoid adenocarcinoma of the stomach mimicking hepatocellular carcinoma: Dynamic computed tomography findings

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Abstract

AIM: To evaluate the dynamic computed tomography (CT) findings of liver metastasis from hepatoid adenocarcinoma of the stomach (HAS) and compared them with hepatocellular carcinoma (HCC).

METHODS: Between January 2000 and January 2015, 8 patients with pathologically proven HAS and liver metastases were enrolled. Basic tumor status was evaluated for the primary tumor location and metastatic sites. The CT findings of the liver metastases were analyzed for tumor number and size, presence of tumor necrosis, hemorrhage, venous tumor thrombosis, and dynamic enhancing pattern.

RESULTS: The body and antrum were the most common site for primary HAS ($n = 7$), and observed metastatic sites included the liver ($n = 8$), lymph nodes ($n = 7$), peritoneum ($n = 4$), and lung ($n = 2$). Most of the liver metastases exhibited tumor

necrosis regardless of tumor size. By contrast, tumor hemorrhage was observed only in liver lesions larger than 5 cm ($n = 4$). Three patterns of venous tumor thrombosis were identified: direct venous invasion by the primary HAS ($n = 1$), direct venous invasion by the liver metastases ($n = 7$), and isolated portal vein tumor thrombosis ($n = 2$). Dynamic CT revealed arterial hyperattenuation and late phase washout in all the liver metastases.

CONCLUSION: On dynamic CT, liver metastasis from HAS shared many imaging similarities with HCC. For liver nodules, the presence of isolated portal vein tumor thrombosis and a tendency for tumor necrosis are imaging clues that suggest the diagnosis of HAS.

Key words: Computed tomography; Liver; Hepatoid adenocarcinoma; Hepatocellular carcinoma; Stomach

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Core tip: Hepatoid adenocarcinoma of the stomach (HAS) is a rare form of gastric cancer with clinicopathological presentation mimicking hepatocellular carcinoma (HCC). The high similarity between the two diseases makes the differential diagnosis challenging, especially when the primary tumor is unknown, and the liver nodules are the only initial finding. In the present study, identical dynamic enhancing pattern (arterial hyperattenuation and late phase washout) between liver metastasis from HAS and HCC was confirmed. Moreover, the presence of isolated portal vein tumor thrombosis and a tendency of tumor necrosis are the imaging clues that suggest the diagnosis of HAS rather than HCC.

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INTRODUCTION

Hepatoid adenocarcinoma of the stomach (HAS) is a rare form of gastric cancer with clinicopathological presentation mimicking hepatocellular carcinoma (HCC). Clinically, the neoplasm is characterized by a predilection for older age, high serum alpha-fetoprotein (AFP) levels, an aggressive clinical course, and poor prognosis^[1]. The aggressive tumor behavior makes the liver metastasis being as the first clinical manifestation in more than 75% of HAS patients^[2]. Pathologically, hepatoid morphology, immunoreactivity with AFP, and a tendency for vascular permeation are the shared features of HAS and HCC^[3]. The high similarity between the two

diseases makes differential diagnosis challenging, especially when the primary tumor is unknown, and the liver nodules are the only initial finding. Moreover, the role of dynamic computed tomography (CT) in liver metastasis from HAS is not well established. To our knowledge, only one case report mentioned a similar dynamic enhancing pattern in liver metastasis from HAS and HCC^[4]. The aim of our study was to evaluate the dynamic CT findings of liver metastasis from HAS and compare them with the typical imaging findings of HCC. The clinical presentation and treatment results of HAS are also evaluated.

MATERIALS AND METHODS

Patient population

Institutional Review Board approval was obtained, and the need for patient informed consent was waived because of the retrospective and anonymous nature of this study. A retrospective search of January 2000 to January 2015 revealed 11 patients with pathologically proven HAS and liver metastases in our institution. Three patients were excluded because their CT studies were not available for review. Finally, 8 patients (6 men and 2 women; mean age 68.5 ± 6.1 years; range 60-78 years) constituted our study cohort. Clinical data including patient demographics, initial presentation, personal history (alcohol use and hepatitis infection), laboratory data (hemoglobin level and serum AFP level), treatments received, and therapeutic result were reviewed.

CT acquisition

CT examinations were requested in regard to clinical symptoms, abnormal liver ultrasound results, or abnormal endoscopic findings. Four patients underwent three-phase dynamic CT of the liver, 2 patients underwent two-phase dynamic CT for gastric tumor staging, and routine abdominal CT was arranged for the remaining 2 patients. Each patient received 100 mL of a nonionic, low-osmolar contrast material (Iohexol, Omnipaque, GE Healthcare, Milwaukee, WI, United States) administered intravenously at a rate of 2.5-3.0 mL/s. Dynamic CT scanning was conducted at 30 s (arterial phase) and 60 s (portal venous phase) after the beginning of intravenous injection. Additional scanning at 3 min (equilibrium phase) was included in the protocol of dynamic CT of the liver. For patients that underwent CT for gastric tumor staging, a total of 800-1000 mL of tap water was administered orally to obtain gastric distension just prior to scanning. Images were routinely reconstructed into coronal and sagittal planes and available for viewing on a picture-archiving and communication system (PACS, GE Healthcare, Milwaukee, WI, United States).

Statistical analysis

CT images were retrospectively reviewed by two

Table 1 Clinical features of hepatoid adenocarcinoma of the stomach

Case No.	Sex/age (yr)	Initial presentation	Location (largest size, cm)	Metastasis	Serum AFP (ng/mL)	Treatment	Follow-up status
1	M/64	Epigastric discomfort	Body, antrum (7.5)	Liver Peritoneum Perigastric lymph nodes	1133.7	Gastrectomy Chemotherapy TACE for liver metastases	Died at 19 mo
2	M/69	Body weight loss	Antrum (7.3)	Liver Lung	281.1	Gastrectomy Chemotherapy	Died at 3 mo
3	M/78	Epigastric discomfort	Antrum (4.5)	Liver Perigastric lymph nodes	3124.9	Gastrectomy Chemotherapy	Died at 5 mo
4	M/63	Epigastric discomfort	Cardia (5.2)	Liver Peritoneum Perigastric lymph nodes	2170.3	Chemotherapy TACE for liver metastases	Died at 6 mo
5	F/70	Palpable mass	Body, antrum (3.8)	Liver Perigastric lymph nodes	890.3	Chemotherapy TACE for liver metastases	Died at 23 mo
6	F/69	Epigastric discomfort	Body, antrum (7.5)	Liver Perigastric lymph nodes	6442.6	Chemotherapy	Died at 9 mo
7	M/60	Epigastric discomfort	Antrum (4.5)	Liver Peritoneum Paraaortic lymph nodes Perigastric lymph nodes	1419.7	Chemotherapy	Died at 3 mo
8	M/75	Body weight loss	Body (4.0)	Liver Lung Peritoneum Perigastric lymph nodes	2904.5	Supportive care	Died at 3 mo

M: Male; F: Female; AFP: Alpha-fetoprotein; TACE: Transarterial chemoembolization.

board-certified radiologists in consensus. Basic tumor status was evaluated for the primary tumor location, tumor size, and metastatic sites (for both nodal metastasis and distant metastasis). Image findings of liver metastases were analyzed for the following factors: tumor number and size, presence of tumor necrosis, hemorrhage, venous tumor thrombosis, and dynamic enhancing pattern. The presence of a gastric tumor was suggested when the gastric wall was 6 mm or greater in thickness or with abnormal contrast enhancement^[5]. Lymph node involvement was considered as present when the short-axis diameter is larger than 8 mm for perigastric lymph nodes and larger than 10 mm for distant lymph nodes^[6,7]. The attenuation of tumor content was analyzed as Hounsfield units^[4] when a region of interest was placed in the center of the lesion. The presence of a low-attenuation (10-30 HU), nonenhancing area within the tumor was defined as tumor necrosis^[8]. By contrast, tumor hemorrhage was considered as a high-attenuation (50-100 HU), nonenhancing area within the tumor^[9]. Venous tumor thromboses, including those of the portal veins, hepatic veins, inferior vena cava, and perigastric veins, were judged by identifying intravenous filling defects with enlargement of the involved venous segment and with minimal contrast enhancement on portal venous phase of CT^[10-12]. Isolated portal vein tumor thrombosis was defined as the presence of tumor thrombosis of the portal vein without evidence of liver

metastasis of the ipsilateral liver lobe^[13]. The degree of tumor attenuation (hypoattenuation, isoattenuation, and hyperattenuation) on CT studies was determined by the largest lesion against the background of the adjacent normal liver parenchyma on arterial phase and late phase (portal venous and equilibrium phases) images^[14]. Heterogeneously enhancing lesions were classified as hyperattenuating when most of the solid component was well-enhanced^[15]. Washout was defined as occurring when any part of the lesion that was hyperattenuating on arterial phase images exhibited a corresponding hypoattenuating area on late phase images^[14].

RESULTS

Clinical findings

Table 1 summarizes the relevant clinical information and basic tumor status of the enrolled patients. Among the 8 patients with pathologically proven HAS and liver metastasis, 6 were male and the mean age at diagnosis was 68.5 ± 6.1 years. All patients were serologically negative for hepatitis B and C, had no history of alcohol abuse, and did not exhibit any clinical or imaging signs of liver cirrhosis. Markedly elevated serum AFP levels (mean 2295.9 ± 1942.8 ng/mL; range 281.1-6442.6 ng/mL) and various degrees of anemia (mean 8.3 ± 0.9 g/dL; range 6.8-9.4 g/dL) were the main laboratory abnormalities. In 4 patients, the symptoms (epigastric discomfort and palpable

Table 2 Computed tomography features of liver metastases from hepatoid adenocarcinoma of the stomach

Case No.	Tumor location	Tumor number (largest size, cm)	Necrosis	Hemorrhage	Venous tumor thrombus	Dynamic enhancing pattern
1	Lateral segment	Single (9.7)	Yes	No	Left portal vein Left hepatic vein Inferior vena cava	Arterial hyperattenuation Late phase washout
2	Bilateral lobes	Multiple (8.7)	Yes	Yes	Right portal vein Left hepatic vein Inferior vena cava	Arterial hyperattenuation Late phase washout
3	Segment 7	Single (2.1)	Yes	No	Right portal vein	NA
4	Right lobe	Multiple (2.8)	Yes	No	Right portal vein Left portal vein ¹	Arterial hyperattenuation Late phase washout
5	Segment 4	Single (7.2)	Yes	No	nil	Arterial hyperattenuation Late phase washout
6	Right lobe	Multiple (9.8)	Yes	Yes	Right portal vein Left portal vein ¹ Gastroepiploic vein ²	Arterial hyperattenuation Late phase washout
7	Bilateral lobes	Multiple (7.5)	Yes	Yes	Right portal vein Left hepatic vein	Arterial hyperattenuation Late phase washout
8	Bilateral lobes	Multiple (8.1)	Yes	Yes	Left portal vein	NA

¹Isolated portal vein tumor thrombosis; ²By direct invasion of primary hepatoid adenocarcinoma of the stomach. NA: Not available.

mass) led to the ultrasonographic detection of hepatic nodules as the initial clinical finding. Only 25% of the patients ($n = 2$) underwent endoscopy prior to CT examinations. The metastatic tumor status made Fluorouracil (5-FU)-based chemotherapy being as the main treatment for most of the patients ($n = 7$). Three patients complicated with gastric outlet obstruction were treated with palliative distal gastrectomy, and transarterial chemoembolization (TACE) with Lipiodol and Doxorubicin infusion was performed for liver metastases in 3 patients. Supportive care was suggested for one patient because of poor performance status. The mean survival time from the first diagnosis was 8.9 ± 7.8 mo (range 3-23 mo).

CT findings

The body and antrum were the most common site for primary HAS ($n = 7$; mean size 5.5 ± 1.6 cm), and the observed metastatic sites included the liver ($n = 8$), lymph nodes ($n = 7$), peritoneum ($n = 4$), and lung ($n = 2$). Table 2 summarizes the CT characteristics of the liver metastases from HAS. Liver metastases usually presented as multiple nodules with variable sizes ($n = 5$), but single presentation was also noted ($n = 3$). Most of the liver metastases exhibited tumor necrosis regardless of tumor size. By contrast, tumor hemorrhage was observed only in liver lesions larger than 5 cm ($n = 4$). Venous tumor thrombosis was identified in 7 patients, and the locations included the portal veins ($n = 7$), hepatic veins ($n = 3$), inferior vena cava ($n = 2$), and gastroepiploic vein ($n = 1$). Three patterns of venous tumor thrombosis were found: direct venous invasion by the primary HAS ($n = 1$), direct venous invasion by the liver metastases ($n = 7$), and isolated portal vein tumor thrombosis ($n = 2$). Dynamic CT revealed arterial hyperattenuation and late phase washout in all the liver metastases.

DISCUSSION

The typical dynamic enhancing pattern of HCC is arterial hyperattenuation followed by washout on late phase images^[16]. This pattern is consistent with a multistep process of hepatocarcinogenesis, which results in tumor vascular changes toward a predominant hepatic arterial supply with a lack of portal venous inflow^[17,18]. According to the diagnostic guidelines of the American Association for the Study of Liver Diseases in 2010^[19], in patients with cirrhosis or chronic hepatitis B, liver nodules larger than 1 cm with typical enhancing pattern on contrast-enhanced CT can be considered HCC and the need for biopsy is obviated. In our study, all the liver metastases from HAS presented with arterial hyperattenuation and washout on dynamic CT studies (Figures 1 and 2). The identical dynamic enhancing pattern, accompanied with high serum AFP levels, makes liver metastasis from HAS a great mimic of HCC. Clinically, HAS is characterized by the absence of risk factors for HCC^[20]. However, in endemic areas with a high incidence of chronic hepatitis B, chronic hepatitis C, and cirrhosis, a HAS patient being a hepatitis carrier or cirrhotic patient simultaneously may not be rare^[21].

In our study, most of the liver metastases from HAS exhibited tumor necrosis regardless of tumor size. Central necrosis can be detected even in liver nodules with a diameter of less than 1 cm (Figure 1). By contrast, spontaneous central necrosis occurs only in HCCs larger than 3 cm^[22], and the reported necrosis rate for HCC is relatively low (10%-40%)^[23]. For liver metastases from HAS, the high incidence of tumor necrosis is believed to be due to outgrowth of the blood supply by the tumor causing hypoxia and subsequent necrosis at the center of the tumor^[24].

The tendency for tumor hemorrhage was a shared

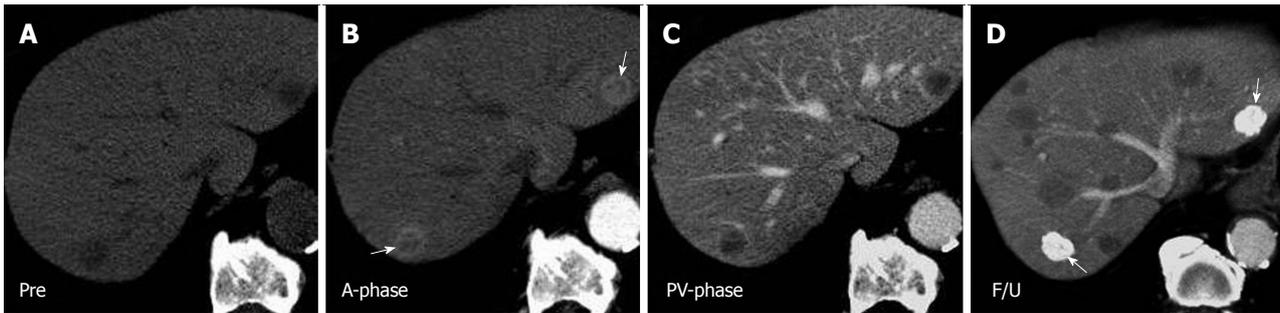


Figure 1 Dynamic enhancing pattern of the liver metastasis from hepatoid adenocarcinoma of the stomach in a 63-yr-old male. A: Liver metastases from hepatoid adenocarcinoma of the stomach presented with hypoattenuation on precontrast computed tomography (CT); B and C: The nodules revealed arterial hyperattenuation (B) and late phase washout (C) on dynamic CT study. Central necrosis (arrows) was found in the small liver nodules; D: The patient received transarterial chemoembolization for liver metastases. The treated liver nodules were well embolized by densely packed Lipiodol (arrows). However, new liver metastases were observed on follow-up CT. Pre: Precontrast; A-phase: Arterial phase; PV-phase: Portal venous phase; F/U: Follow-up image.

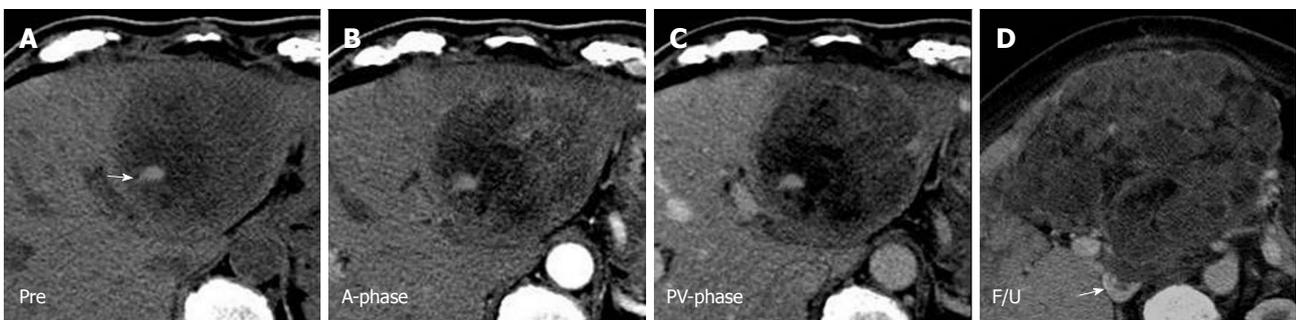


Figure 2 Dynamic enhancing pattern of the liver metastasis from hepatoid adenocarcinoma of the stomach in a 69-yr-old male. A: Liver metastasis from hepatoid adenocarcinoma of the stomach presented with hypoattenuation on precontrast computed tomography (CT); B and C: The liver mass revealed arterial hyperattenuation (B) and late phase washout (C) on dynamic CT study. Central necrosis and tumor hemorrhage (arrow) were noted; D: The patient received total gastrectomy combined with systemic chemotherapy. Progression of the liver metastasis with direct IVC invasion (arrow) was observed on follow-up CT. Pre: Precontrast; A-phase: Arterial phase; PV-phase: Portal venous phase; F/U: Follow-up image.

feature between liver metastasis from HAS and HCC. In our study, tumor hemorrhage was observed only in liver lesions larger than 5 cm (Figure 2). Similarly, HCC with a larger diameter carried a higher risk of tumor hemorrhage^[25]. Intratumoral bleeding is usually a result of local ischemia caused by rapid growth of the lesion^[26]. In 3%-26% of patients with HCC, hemoperitoneum occurs after tumor bleeding^[27,28]. By contrast, neither hemoperitoneum nor tumor rupture has been reported in patients with HAS.

Lee *et al*^[7] proposed two patterns of liver metastasis from HAS: a dominant bulky mass with adjacent portal vein tumor thrombosis and multiple nodules of a similar size without tumor thrombosis. The dominant bulky mass pattern was reported to be more common. In our study, a predilection existed for a dominant bulky mass (Figures 2 and 3). However, the tumor number and size were unrelated to the presence of portal vein tumor thrombosis. On CT images, most of the tumor thromboses were caused by direct venous invasion of the metastatic liver tumors (Figure 3C). Similarly, most of the reported venous tumor thromboses in HCC were caused by direct tumor invasion^[29]. In one patient with gastroepiploic vein tumor thrombosis, the tendency for vascular

permeation by the primary HAS was demonstrated. This finding supports those of two previous studies^[4,7]. Moreover, our study demonstrated a unique type of venous tumor thrombosis: isolated portal vein tumor thrombosis (Figure 3D). This finding implies a possible route of tumor spread for the primary HAS and could be useful in differential diagnosis.

A percutaneous liver biopsy is usually performed as a problem-solving tool on liver nodules of uncertain nature. However, the procedure may play a limited role in differentiation between liver metastasis from HAS and HCC. HAS shares strikingly morphologic similarity with HCC in histology^[20]. Routine immunohistochemical stains, like AFP, HepPar1, and GPC-3, are useful but not specific for differential diagnosis^[21]. Although some novel immunohistochemical markers, such as PIVKA-II^[30], CEA, PLUNC, and CK19^[3], have exhibited varying degrees of ability in differentiation, they are performed only upon adequate clinical and imaging suspicions of HAS. By contrast, for patients with suspected HAS and liver metastasis, liver biopsy along with endoscopic biopsy can be performed to confirm the identical tumor origin in both the liver and stomach, and exclude the diagnosis of synchronous HCC and gastric cancer, which is the most crucial differential diagnosis.

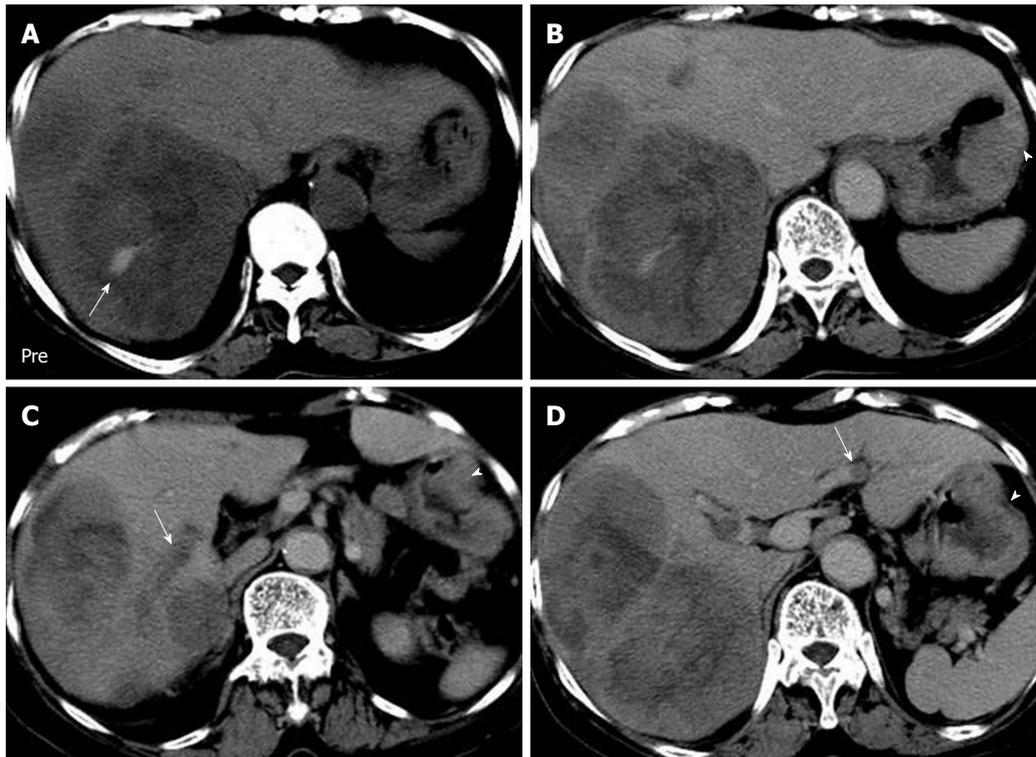


Figure 3 Venous tumor thrombosis in a 69-yr-old female with hepatoid adenocarcinoma of the stomach and liver metastases. A: Bulky liver metastases presented with tumor hemorrhage (arrow) on precontrast computed tomography; B and C: Eccentric wall thickening and heterogenous enhancement of the gastric body (arrowheads) implied gastric malignancy. On portal venous phase, the liver mass presented irregular central necrosis (B) and right portal vein tumor thrombosis (arrow; C); D: Isolated left portal vein tumor thrombosis (arrow) was observed. No visible liver nodule was found at the left liver lobe. Pre: Precontrast.

The prognosis of HAS is extremely poor, mainly resulting from the strong tendency for vascular permeation and early distant metastases^[4]. Aggressive treatments, such as radical surgery combined with chemotherapy, have been proven to positively affect the clinical outcome of HAS patients^[31,32]. Moreover, because striking pathological similarities are shared by HAS and HCC, the treatments recommended for HCC may also be effective for HAS. Petrelli *et al.*^[33] suggested Sorafenib (Nexavar, Bayer HealthCare, Montville, NJ, United States) as a possible treatment for hepatoid adenocarcinoma. In our study, TACE was performed along with 5-FU-based systemic chemotherapy in 3 patients. Most of the treated liver nodules were well embolized by densely packed Lipiodol. However, new liver metastases were observed on follow-up CT (Figure 1D), which may be contributed by the continuous tumor spread from the poorly controlled primary HAS through the portal venous system. Our results suggest that TACE, similarly to its role in HCC treatment, may serve as a local therapy for liver nodules of HAS but must be accompanied with systemic chemotherapy or radical surgery for complete tumor control.

The presence of gastric malignancy was not always easily identified on CT images. The detectability of primary HAS was influenced by morphologic features, the thickness of the gastric wall, and the degree of tumor enhancement. Moreover, abdominal CT studies

performed as a result of nonspecific initial symptoms or abnormal liver ultrasonographic findings would not follow the standard protocol for gastric tumor staging and would thus impair the detectability of gastric malignancy on CT. D'Elia *et al.*^[34] reported conventional CT studies possess a low range of detectability (40%–90%) in preoperative gastric cancer staging. When the primary tumor is unknown, and the liver nodules are the only initial finding, correct diagnosis of HAS can be challenging.

This study has some limitations. First, it is a single-center, retrospective, and nonrandomized study. Because of the rarity of HAS, only 8 patients were enrolled in this study. The small sample size may limit accurate analysis and lead to bias of the results. Second, the presence of venous tumor thrombosis, central necrosis, and intratumoral bleeding was determined according to the imaging criteria, not by histologic proof. However, all the enrolled patients had their HAS confirmed histologically through an operation or biopsy and had no other conditions predisposing them to portal venous thrombosis. Third, this study covered patients over a span of 15 years. Images from different CT scanner with various parameters were included for review. However, this was not a major limitation since the intra-abdominal lesions were usually bulky.

In conclusion, liver metastasis from HAS shared many CT imaging similarities with HCC. For the liver

nodules, the presence of isolated portal vein tumor thrombosis and a tendency for tumor necrosis are imaging clues that suggest the diagnosis of HAS. Liver biopsy along with endoscopic biopsy can be performed to confirm the identical tumor origin in both the liver and stomach for the patients with suspicious HAS.

COMMENTS

Background

Hepatoid adenocarcinoma of the stomach (HAS) is a rare gastric cancer with clinicopathological presentation mimicking hepatocellular carcinoma (HCC). The high similarity between the two diseases makes differential diagnosis challenging, especially when the primary tumor is unknown, and the liver nodules are the only initial finding. Moreover, the role of dynamic computed tomography (CT) in liver metastasis from HAS is not well established.

Research frontiers

To date, only one case report mentioned the dynamic enhancing pattern in liver metastasis from HAS and HCC. This study was designed to evaluate the dynamic CT findings of liver metastasis from HAS and compare them with the typical imaging findings of HCC.

Innovations and breakthroughs

Identical dynamic enhancing pattern (arterial hyperattenuation and late phase washout) between liver metastasis from HAS and HCC was confirmed in the present study. Moreover, most of the liver metastases from HAS exhibited tumor necrosis regardless of tumor size. Isolated portal vein tumor thrombosis, a unique type of venous tumor thrombosis, implies a possible route of tumor spread for the primary HAS and could be useful in differential diagnosis.

Applications

The presence of isolated portal vein tumor thrombosis and a tendency of tumor necrosis are the imaging clues that suggest the diagnosis of HAS rather than HCC.

Terminology

HAS is a rare gastric cancer, which usually presents high serum alpha-fetoprotein (AFP) levels, an aggressive clinical course, and poor prognosis. Pathologically, hepatoid morphology, immunoreactivity with AFP, and a tendency for vascular permeation are the shared features of HAS and HCC.

Peer-review

This is a very good paper.

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