ANTICANCER RESEARCH *41*: 5241-5247 (2021)
doi:10.21873/anticanres.15343

Chemoembolization for Hepatocellular Carcinoma in Patients With Inferior Vena Caval/Right Atrial Tumor Thrombi Without Hepatic Vein Invasion

MINUK KIM[1], HYO-CHEOL KIM[2] and JIN WOOK CHUNG[2]

[1]*Department of Radiology, SMG-SNU Boramae Medical Center, Seoul, Republic of Korea;*
[2]*Department of Radiology, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea*

Abstract. *Aim: To clarify the clinical and radiological features of isolated tumor thrombi in the inferior vena cava (IVC)/right atrium in patients with hepatocellular carcinoma (HCC) without hepatic vein invasion. Patients and Methods: In this retrospective study, from January 2007 to December 2019, a total of 35,163 chemoembolization sessions were performed in 7,704 patients with HCC. Among them, 10 (0.13%) patients had tumor thrombi in the IVC/right atrium without definitive hepatic vein invasion. Computed tomographic (CT) scans, digital subtraction angiograms, and cone-beam CT images were retrospectively reviewed and interpreted. Results: The tumor thrombi were supplied by the right inferior phrenic artery (n=8) or the right internal mammary artery (n=2). Follow-up CT scans in eight patients showed linear accumulation of iodized oil along the diaphragm, which was presumed to be a thrombosis of the phrenic vein. Retrospective review of formal radiological reports of pre-procedural CT scans revealed that a correct diagnosis of tumor thrombi of the IVC/right atrium was made in only three cases. Conclusion: HCC invading the phrenic vein may have tumor thrombi in the IVC/right atrium without hepatic vein invasion.*

Hepatocellular carcinoma (HCC) is the most common primary malignant liver tumor and often invades the portal vein (1). The hepatic vein is infrequently involved, and tumor thrombi are seldom detected in the inferior vena cava (IVC) or right atrium (2). Although patients with HCC with IVC/right atrial tumor thrombi have bleak prognoses and systemic therapy is a standard treatment option, local treatments, such as surgery, external radiotherapy, and chemoembolization, have been increasingly performed in these patients (3-6).

Most tumor thrombi in the IVC and right atrium develop as continuous extensions of tumor thrombi in the hepatic veins (2) but there are occasional reports of isolated right atrium metastasis without hepatic vein invasion (7, 8). A recent report presented cases in which the tumor thrombi of the IVC/right atrium extended to the phrenic vein, as confirmed by surgical resection (9). We have infrequently encountered patients with HCC with IVC/right atrial thrombi without hepatic venous thrombi who were treated with chemoembolization. Our hypothesis is that HCC can directly invade the diaphragm and the phrenic vein, resulting in tumor thrombi in the IVC and/or right atrium. The purpose of this study was to clarify the clinical and radiological features of isolated tumor thrombi in the IVC/right atrium in patients with HCC without hepatic vein invasion.

Patients and Methods

Patients. The Institutional Review Board approved this retrospective study (no, 2104-112-1212), and the requirement for informed patient consent was waived. From January 2007 to December 2019, a total of 35,163 chemoembolization sessions were performed in 7,704 patients with HCC. Among them, 10 (0.13%) patients had tumor thrombi in the IVC/right atrium without definite hepatic vein invasion. This study population consisted of eight men and two women (mean age=68.6 years, range=55-80 years) (Table I).

All 10 patients had a previous history of treatment for HCC, including chemoembolization (n=9), sorafenib (n=6), radiofrequency ablation (n=6), external radiation therapy (n=6), percutaneous alcohol injection (n=3), and surgical resection (n=3). Of the 10 patients, nine had previous chemoembolization (median=8 sessions; range=1-22 sessions), and seven patients had been previously treated with chemoembolization in the right inferior phrenic artery. The time interval between the initial HCC diagnosis

Correspondence to: Hyo-Cheol Kim, MD, Department of Radiology, Seoul National University Hospital, #101 Daehak-ro, Jongno-gu, Seoul, 03080, Korea. Tel: +82 220722584, Fax: +82 27436385, e-mail: angiointervention@gmail.com

Key Words: Hepatocellular carcinoma, chemoembolization, right atrium thrombus, inferior vena cava thrombus, inferior phrenic vein.

Table I. *Summary of clinical and radiological findings of 10 patients with hepatocellular carcinoma.*

			Previous treatment			CE for IVC/RA tumor							
Patient no.	Gender/ age	Etiology	Previous treatment except CE	No. of previous CEs	CE via extrahepatic collateral arteries	Interval from initial diagnosis to treatment, years	Child–Pugh class	Size of tumor thrombi	Extent of tumor thrombi	Feeding artery	Formal radiologic report	Response of IVC/RA tumor	Follow-up period after CE, months
1	M/68	HBV	Op, PEI, RFA	15	RIPA, ICA	7.3	A5	2.6	IVC/RA	RIMA	Myxoma	CR	59
2	M/63	HBV	Op, external RT, sorafenib	6	No	4.5	A5	1.9	IVC	RIPA	Not mentioned	PR	10
3	M/72	HBV	RFA	0	No	3.5	A5	3.1	IVC/RA	RIPA	Not mentioned	PR	21
4	F/71	HBV	PEI, RFA, External RT	9	RIPA, ICA	4.9	A6	1.5	IVC	RIPA	Not mentioned	CR	17
5	M/67	HBV	RFA, External RT, sorafenib	1	No	3.2	A5	2.9	IVC/RA	RIPA	Not mentioned	CR	15
6	F/80	HBV	RFA	8	RIPA	4.5	A6	1.0	IVC	RIPA	Tumor thrombi	PR	9
7	M/77	HBV	sorafenib, external RT	7	RIPA, RCA	4.2	B7	2.0	IVC/RA	RIPA	Tumor thrombi	SD	11
8	M/73	HBV	Op, external RT, Sorafenib	5	RIPA	5	A6	1.6	IVC	RIMA	Tumor thrombi	CR	6
9	M/55	HBV	sorafenib	11	RIPA, RCA, LIPA, omental branch	2.8	A5	2.1	IVC/RA	RIPA	Not mentioned	PR	20
10	M/66	HBV	RFA, PEI, sorafenib	22	RIPA	12.2	A6	1.0	IVC	RIPA	Not mentioned	PR	12

CE: Chemoembolization; CR: complete response; F: female; HBV: hepatitis B virus; ICA: intercostal artery; IVC: inferior vena cava; LIPA: left inferior phrenic artery; M: male; Op: surgical resection; PEIT: percutaneous alcohol injection; PR: partial response; RA: right atrium; RCA: renal capsular artery; RFA: radiofrequency ablation; RIMA: right internal mammary artery; RIPA: right inferior phrenic artery; RT: radiation therapy; SD: stable disease.

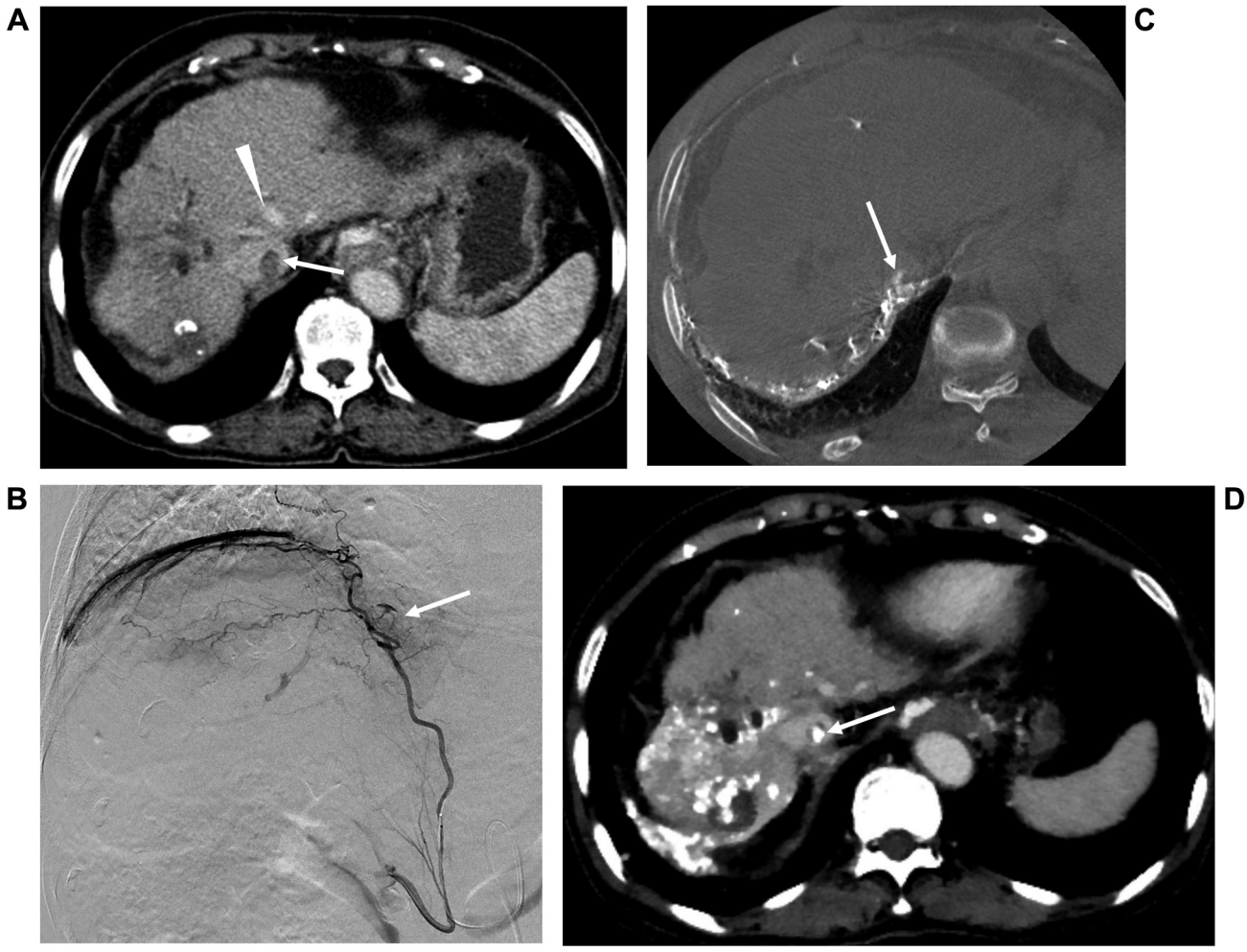

Figure 1. *An 80-year-old woman (patient number 6) with hepatocellular carcinoma. A: Computed tomography (CT) scan showed a small thrombus (arrow) in the inferior vena cava (IVC) below the hepatic vein confluence. Note the patent hepatic vein (arrowhead). B: Right inferior phrenic angiogram showing tumor blush (arrow). C: Axial image of cone beam CT of the right inferior phrenic artery showing enhancement of a tumor thrombus (arrow). D: CT scan 1 month after chemoembolization showing partial accumulation of iodized oil in a thrombus (arrow).*

and chemoembolization of the tumor thrombi of the IVC/right atrium ranged from 2.8 to 12.2 years.

Chemoembolization procedure. For all patients, enhanced dynamic computed tomographic (CT) scans (pre-contrast, hepatic arterial, portal venous, and equilibrium phase) of the liver were obtained before chemoembolization. Detailed protocols for CT imaging were described previously (10). All chemoembolization procedures were performed by, or under the supervision of, two experienced interventional radiologists (H.C.K. and J.W.C., with 14 and 28 years of experience in interventional oncology, respectively). A 5.0 Fr catheter was used for celiac arteriography, and various 1.7 Fr–2.0 Fr microcatheters (Progreat - Terumo, Tokyo, Japan; Carnelian - Tokai Medical Products, Kasugai, Japan; Veloute - Asahi intecc, Aichi, Japan; and Radiostar - Taewoong Medial, Gimpo, Republic of Korea) were used for selective arteriography.

An emulsion of 2-10 ml iodized oil (Lipiodol; Andre Guerbet, Aulnay-sous-Bois, France) and 10-50 mg doxorubicin hydrochloride (Adriamycin RDF; Ildong Pharmaceutical, Seoul, Republic of Korea) was infused into the tumor-feeding branch as selectively as possible. Then additional embolization was performed with absorbable gelatin sponge particles (Gelfoam - Upjohn, Kalamazoo, MI, USA; Cutanplast - Mascia Brunelli, Milan, Italy; or EG gel - Engain, Seongnam, Republic of Korea) to achieve near or complete stasis of the target vessels. For the target vessels involved in tumor thrombosis, 50-100 mg cisplatin was additionally infused at a rate of 2-5 mg/min (11).

Cone-beam CT images were obtained at the hepatic artery and extrahepatic collateral arteries using a flat-panel detector angiography unit (Axiom Artis dTA/VB30, Artis zee or Artis Q; Siemens, Erlangen, Germany). Detailed protocols for cone beam CT were described previously (12).

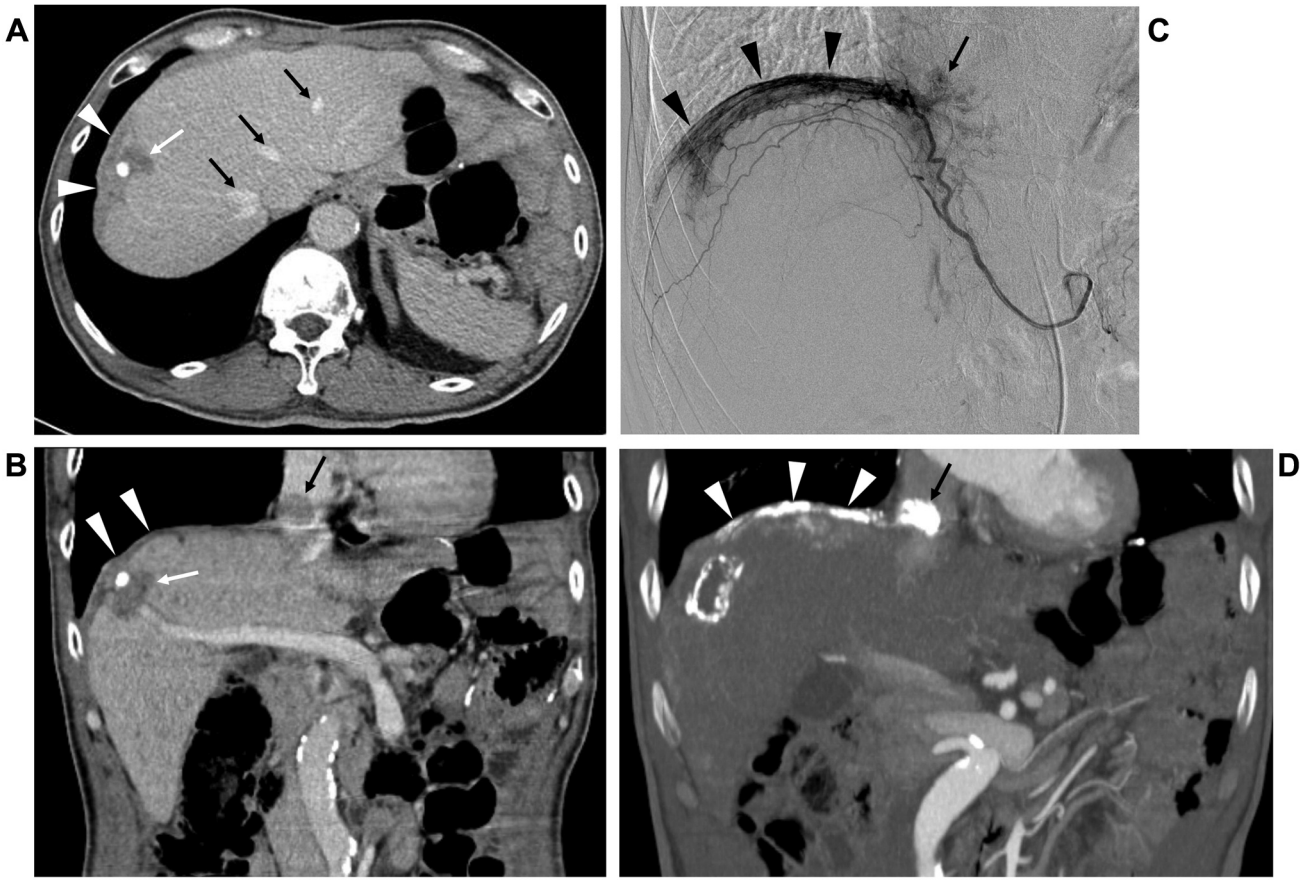

Figure 2. *A 67-year-old man (patient number 5) with hepatocellular carcinoma. A: Computed tomography (CT) scan showing diffuse thickening of the diaphragm (arrowheads). Note the patent hepatic vein (black arrows) and previously treated tumor with radiofrequency ablation (white arrow). B: Reformatted image of a coronal CT scan showing diffuse thickening of the diaphragm (arrowheads). Note the tumor thrombus in the right atrium (black arrow) and tumor previously treated with radiofrequency ablation (white arrow). C: Right inferior phrenic angiogram showing diffuse tumor blush (arrowheads) suggesting diaphragmatic metastasis and a right atrial tumor thrombus (arrow). D: CT scan 1 month after chemoembolization showing diffuse accumulation of iodized oil in the diaphragm (arrowheads) and a right atrial tumor thrombus (arrow).*

Analysis. CT scans, digital subtraction angiograms, and cone-beam CT images were retrospectively reviewed and interpreted by consensus between the two authors (M.K, H.C.K), and the patients' medical records were reviewed by one author (M.K.). Formal radiological reports of CT scans were also reviewed to check whether tumor thrombi in the IVC or right atrium were mentioned.

Because contrast media and unopacified blood were mixed in the IVC and heart, it was not possible to evaluate the size and viability of the tumor thrombi on the hepatic arterial or portal venous phase images. The size and viability of the tumor thrombi were assessed based on the equilibrium phase images. Because conventional chemoembolization was performed, the areas where Lipiodol did not accumulate were considered as viable tumor thrombi. Using the enhanced CT scan of the first follow-up, the response of tumor thrombi in the IVC and right atrium was evaluated and categorized as complete response, partial response, stable disease, or progressive disease. A complete response was observed when Lipiodol accumulated in the whole tumor thrombus in the IVC/right atrium. A partial response was observed when the viable portion (area where Lipiodol did not accumulate) decreased by at least 30% in diameter. Progressive disease was observed when the viable portion increased by at least 20% in diameter. Stable disease was defined as cases that did not exhibit either partial response or progressive disease.

Results

The maximum diameter of the tumor thrombi of the IVC/right atrium ranged from 1.0 to 3.1 cm (median=1.95 cm). Tumor thrombi extended to the IVC (n=5) (Figure 1A) or right atrium (n=5) (Figure 2B and Figure 3A). Tumor thrombi in the IVC joined the IVC above the hepatic vein confluence in nine and below it in one (Figure 1A). Multifocal intrahepatic viable tumors were observed in nine patients, and one patient (patient number 5) had only diaphragmatic thickening without a viable intrahepatic tumor. Diffuse thickening of the diaphragm, suggesting diaphragmatic metastasis, was noted in two

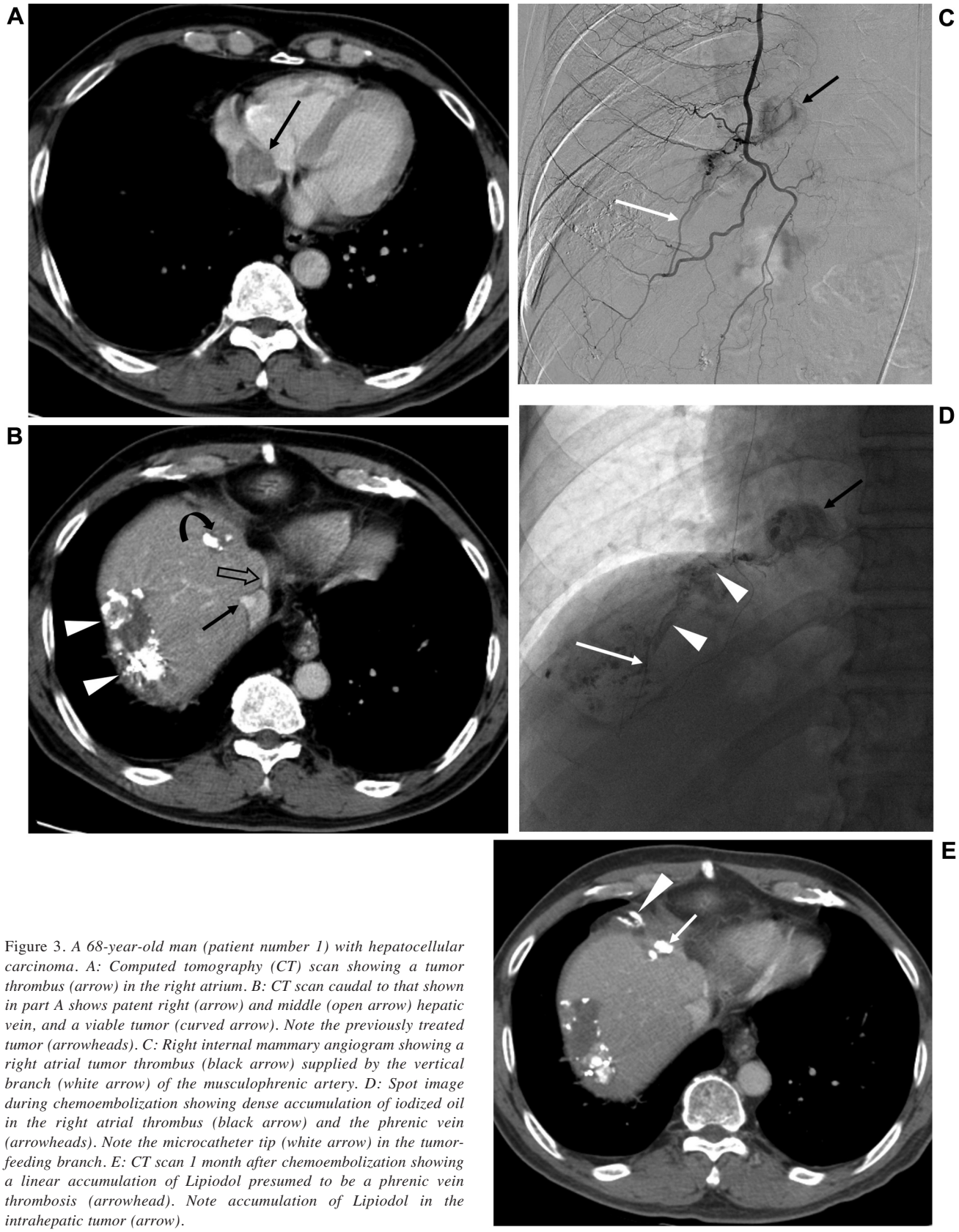

Figure 3. *A 68-year-old man (patient number 1) with hepatocellular carcinoma. A: Computed tomography (CT) scan showing a tumor thrombus (arrow) in the right atrium. B: CT scan caudal to that shown in part A shows patent right (arrow) and middle (open arrow) hepatic vein, and a viable tumor (curved arrow). Note the previously treated tumor (arrowheads). C: Right internal mammary angiogram showing a right atrial tumor thrombus (black arrow) supplied by the vertical branch (white arrow) of the musculophrenic artery. D: Spot image during chemoembolization showing dense accumulation of iodized oil in the right atrial thrombus (black arrow) and the phrenic vein (arrowheads). Note the microcatheter tip (white arrow) in the tumor-feeding branch. E: CT scan 1 month after chemoembolization showing a linear accumulation of Lipiodol presumed to be a phrenic vein thrombosis (arrowhead). Note accumulation of Lipiodol in the intrahepatic tumor (arrow).*

patients (numbers 3 and 5) who had radiofrequency ablation for tumors abutting the diaphragm. The feeding artery to the tumor thrombi of the IVC/right atrium was the right inferior phrenic artery in eight cases (Figure 1B and Figure 2C) and right internal mammary artery in two (Figure 3C).

The responses of the tumor thrombi in the IVC/right atrium observed in the first follow-up CT scan were complete response in four (Figure 2D), partial response in five (Figure 1D), and stable disease in one. Linear accumulation of iodized oil along the diaphragm was observed in eight patients (Figure 3E). No patients experienced pulmonary embolism related to thrombi of the IVC/right atrium or right heart failure.

Retrospective review of formal radiological reports of pre-procedural CT scans revealed that a correct diagnosis of tumor thrombi of the IVC/right atrium had been made for only three patients. Myxoma was mentioned in the report for one patient, and tumor thrombi were completely missed in six patients.

Discussion

While the left inferior phrenic vein drains into the IVC, left suprarenal vein, left renal vein, or left hepatic vein, according to an anatomical study of 300 cadavers (13), the right inferior phrenic vein drains into the IVC in most cases. A surgical study of 77 patients revealed that the right inferior phrenic vein ran into the IVC just cranially to the right hepatic vein caval confluence (14). Thus, if the right inferior phrenic vein is involved by tumor thrombi, isolated IVC tumor thrombi without hepatic vein thrombosis can develop in patients with HCC.

Lee *et al*. reported that IVC tumor thrombi were frequently supplied by extrahepatic collateral arteries such as the right inferior phrenic, adrenal, or internal mammary arteries (3). The right inferior phrenic artery supplies most of the right hemidiaphragm. Because the right inferior phrenic artery has a branch supplying the IVC (15), it is to be expected that IVC tumor thrombi are fed by the right inferior phrenic artery. If the right inferior phrenic artery is obliterated by previous chemoembolization, adjacent collateral arteries, such as the internal mammary artery, may take over blood supply to the IVC tumor thrombi (3). In this study, the right inferior phrenic artery (n=8) and internal mammary artery (n=2) supplied the IVC/right atrial tumor thrombi.

Based on the formal radiological reports, this study found that tumor thrombi in the IVC/right atrium were missed in 6 out of 10 patients. In hepatic artery and portal venous phase images, contrast media in the heart and unopacified blood coming from the hepatic vein and IVC mingle, resulting in heterogeneous enhancement of the suprahepatic IVC. IVC/right atrial tumor thrombi can mimic this feature, which can be easily overlooked by abdominal radiologists. In addition, without hepatic venous thrombosis, abdominal radiologists can easily miss the presence of the tumor thrombi of the IVC or right atrium.

Standard treatment for HCC with vascular invasion is systemic therapy, such as sorafenib or atezolizumab plus bevacizumab (16). However, in actual practice, some patients with advanced-stage HCC, including those with extrahepatic metastasis, are treated using locoregional treatments, such as chemoembolization, because most patients die of intrahepatic tumor progression (17). In this study, six patients had already received sorafenib due to vascular invasion or extrahepatic metastasis. Thus, chemoembolization may play a role in controlling intrahepatic HCC refractory to systemic therapy. In this study, four patients had dense, complete accumulation of Lipiodol in the tumor thrombi. An objective response of the tumor thrombi was observed in nine patients. Thus, chemoembolization may be effective in controlling tumor thrombi in the IVC or right atrium.

This study has some limitations. Firstly, even though linear accumulation of iodized oil along the diaphragm, which is presumed to be a phrenic vein thrombosis, was observed in eight patients, there was no surgical or pathological confirmation of the right inferior phrenic vein thrombosis. Secondly, because of the small study population, statistical analysis of any clinical and radiological findings was not performed.

In conclusion, when HCC invades the diaphragm or phrenic vein, it may manifest as isolated tumor thrombi in the IVC or right atrium without hepatic vein thrombosis. Tumor thrombi can be supplied by the right inferior phrenic artery or internal mammary artery.

Conflicts of Interest

The Authors have no conflicts of interest to disclose in relation to this study.

Authors' Contributions

Guarantor of integrity of the entire study: Hyo-Cheol Kim. Study concepts and design: Hyo-Cheol Kim. Literature research: Hyo-Cheol Kim, Minuk Kim. Clinical studies: Hyo-Cheol Kim, Minuk Kim, Jin Wook Chung. Data analysis: Hyo-Cheol Kim, Minuk Kim. Manuscript preparation: Minuk Kim. Article editing: Hyo-Cheol Kim, Jin Wook Chung.

References

1 Korean Liver Cancer Association (KLCA) and National Cancer Center (NCC), Goyang, Korea: 2018 Korean Liver Cancer Association-National Cancer Center Korea practice guidelines for the management of hepatocellular carcinoma. Korean J Radiol *20(7)*: 1042-1113, 2019. PMID: 31270974. DOI: 10.3348/kjr.2019.0140

2 Cheng HY, Wang XY, Zhao GL and Chen D: Imaging findings and transcatheter arterial chemoembolization of hepatic

malignancy with right atrial embolus in 46 patients. World J Gastroenterol *14(22)*: 3563-3568, 2008. PMID: 18567087. DOI: 10.3748/wjg.14.3563

3 Lee IJ, Chung JW, Kim HC, Yin YH, So YH, Jeon UB, Jae HJ, Cho BH and Park JH: Extrahepatic collateral artery supply to the tumor thrombi of hepatocellular carcinoma invading inferior vena cava: the prevalence and determinant factors. J Vasc Interv Radiol *20(1)*: 22-29, 2009. PMID: 19026566. DOI: 10.1016/j.jvir.2008.09.030

4 Koo JE, Kim JH, Lim YS, Park SJ, Won HJ, Sung KB and Suh DJ: Combination of transarterial chemoembolization and three-dimensional conformal radiotherapy for hepatocellular carcinoma with inferior vena cava tumor thrombus. Int J Radiat Oncol Biol Phys *78(1)*: 180-187, 2010. PMID: 19926229. DOI: 10.1016/j.ijrobp.2009.07.1730

5 Rim CH, Jeong BK, Kim TH, Hee Kim J, Kang HC and Seong J: Effectiveness and feasibility of external beam radiotherapy for hepatocellular carcinoma with inferior vena cava and/or right atrium involvement: a multicenter trial in Korea (KROG 17-10). Int J Radiat Biol *96(6)*: 759-766, 2020. PMID: 31977276. DOI: 10.1080/09553002.2020.1721607

6 Lee HA and Rim CH: Efficacy of local treatments for hepatocellular carcinoma involving the inferior vena cava and/or right atrium. J Hepatocell Carcinoma *7*: 435-446, 2020. PMID: 33376712. DOI: 10.2147/JHC.S285357

7 Kawakami M, Koda M, Mandai M, Hosho K, Murawaki Y, Oda W and Hayashi K: Isolated metastases of hepatocellular carcinoma in the right atrium: Case report and review of the literature. Oncol Lett *5(5)*: 1505-1508, 2013. PMID: 23760591. DOI: 10.3892/ol.2013.1240

8 Fukuoka K, Masachika E, Honda M, Tsukamoto Y and Nakano T: Isolated metastases of hepatocellular carcinoma in the left atrium, unresponsive to treatment with sorafenib. Mol Clin Oncol *3(2)*: 397-399, 2015. PMID: 25798274. DOI: 10.3892/mco.2014.454

9 Tomita K, Shimazu M, Takano K, Gunji T, Ozawa Y, Sano T, Chiba N, Abe Y and Kawachi S: Resection of recurrent hepatocellular carcinoma with thrombi in the inferior vena cava, right atrium, and phrenic vein: a report of three cases. World J Surg Oncol *18(1)*: 138, 2020. PMID: 32571339. DOI: 10.1186/s12957-020-01914-8

10 Kim BR, Lee JM, Lee DH, Yoon JH, Hur BY, Suh KS, Yi NJ, Lee KB and Han JK: Diagnostic performance of gadoxetic acid-enhanced liver MR imaging versus multidetector CT in the detection of dysplastic nodules and early hepatocellular carcinoma. Radiology *285(1)*: 134-146, 2017. PMID: 28609205. DOI: 10.1148/radiol.2017162080

11 Kim HC, Lee JH, Chung JW, Kang B, Yoon JH, Kim YJ, Lee HS, Jae HJ and Park JH: Transarterial chemoembolization with additional cisplatin infusion for hepatocellular carcinoma invading the hepatic vein. J Vasc Interv Radiol *24(2)*: 274-283, 2013. PMID: 23369561. DOI: 10.1016/j.jvir.2012.11.002

12 Kim HC: Role of C-arm cone-beam CT in chemoembolization for hepatocellular carcinoma. Korean J Radiol *16(1)*: 114-124, 2015. PMID: 25598679. DOI: 10.3348/kjr.2015.16.1.114

13 Loukas M, Louis RG Jr, Hullett J, Loiacano M, Skidd P and Wagner T: An anatomical classification of the variations of the inferior phrenic vein. Surg Radiol Anat *27(6)*: 566-574, 2005. PMID: 16172871. DOI: 10.1007/s00276-005-0029-0

14 Torzilli G, Montorsi M, Palmisano A, Del Fabbro D, Gambetti A, Donadon M, Olivari N and Makuuchi M: Right inferior phrenic vein indicating the right hepatic vein confluence into the inferior vena cava. Am J Surg *192(5)*: 690-694, 2006. PMID: 17071208. DOI: 10.1016/j.amjsurg.2005.10.022

15 Loukas M, Hullett J and Wagner T: Clinical anatomy of the inferior phrenic artery. Clin Anat *18(5)*: 357-365, 2005. PMID: 15971218. DOI: 10.1002/ca.20112

16 Ogasawara S, Choo SP, Li JT, Yoo C, Wang B, Lee D and Chow PKH: Evolving treatment of advanced hepatocellular carcinoma in the Asia-Pacific region: a review and multidisciplinary expert opinion. Cancers (Basel) *13(11)*: 2626, 2021. PMID: 34071818. DOI: 10.3390/cancers13112626

17 Yoo JJ, Lee JH, Lee SH, Lee M, Lee DH, Cho Y, Lee YB, Yu SJ, Kim HC, Kim YJ, Yoon JH, Kim CY and Lee HS: Comparison of the effects of transarterial chemoembolization for advanced hepatocellular carcinoma between patients with and without extrahepatic metastases. PLoS One *9(11)*: e113926, 2014. PMID: 25427152. DOI: 10.1371/journal.pone.0113926

Received July 11, 2021
Revised August 9, 2021
Accepted August 25, 2021