

[ CASE REPORT ]

## Rupture of Hepatic Pseudoaneurysm Formed Nine Years after Carbon Ion Radiotherapy for Hepatocellular Carcinoma

Shuhei Yoshikawa<sup>1</sup>, Takeharu Asano<sup>1</sup>, Mizuki Watanabe<sup>1</sup>, Takehiro Ishii<sup>1</sup>, Haruka Ohtake<sup>1</sup>, Junichi Fujiwara<sup>1</sup>, Masanari Sekine<sup>1</sup>, Takeshi Uehara<sup>1</sup>, Kohei Hamamoto<sup>2</sup>, Kazuhito Yuhashi<sup>1</sup>, Satohiro Matsumoto<sup>1</sup>, Shinichi Asabe<sup>1</sup>, Hiroyuki Miyatani<sup>1</sup>, Katsuhiko Matsuura<sup>2</sup> and Hirosato Mashima<sup>1</sup>

### Abstract:

An 83-year-old man with a history of carbon ion radiotherapy for hepatocellular carcinoma nine years ago presented to a primary care hospital with a fever and abdominal pain. He underwent computed tomography, which revealed the rupture of a hepatic pseudoaneurysm close to the fiducial marker for carbon ion radiotherapy and bleeding into the bile duct. He was successfully treated with transcatheter arterial embolization. Thereafter, re-rupture occurred from a site proximal to the first rupture, and this was treated similarly. It is necessary to be alert for not only tumor recurrence but also pseudoaneurysm occurrence after carbon ion radiotherapy.

**Key words:** pseudoaneurysm, rupture, obstructive jaundice, hepatocellular carcinoma, transcatheter arterial embolization, carbon ion radiotherapy

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### Introduction

Although morbidity of hepatic pseudoaneurysm is rare, the risk of mortality is very high with massive bleeding possible in the case of pseudoaneurysm rupture (1, 2). The major causes of hepatic pseudoaneurysm onset are abdominal trauma and iatrogenesis and occasionally arteriosclerosis. Recently, radiotherapy for hepatocellular carcinoma (HCC) has been safely performed with high-dose radiation and a high local control rate, and improved survival rates have been reported. Carbon ion radiotherapy and proton beam therapy have a high dose concentration, and carbon ion radiotherapy can deliver significantly higher target conformity than conventional radiotherapy while sparing normal liver tissue (3, 4). The major adverse effects of radiotherapy include liver dysfunction, skin disorder, and gastrointestinal

bleeding. However, while the incidence of severe adverse effects with this therapy is low, the total number of reported cases is currently insufficient to draw any definitive conclusions at present. Pseudoaneurysm formation has been reported at the radiation site in a few studies; however, very few studies have been conducted in the late stage, such as a few years after carbon ion radiotherapy.

In the present case, hepatic pseudoaneurysm ruptured nine years after carbon ion radiotherapy for HCC. We herein report the case of a patient who experienced two instances of hepatic pseudoaneurysm rupture into the intrahepatic bile duct, leading to obstructive jaundice.

### Case Report

The patient was an 83-year-old man who presented to a primary care hospital with the chief complaint of a fever

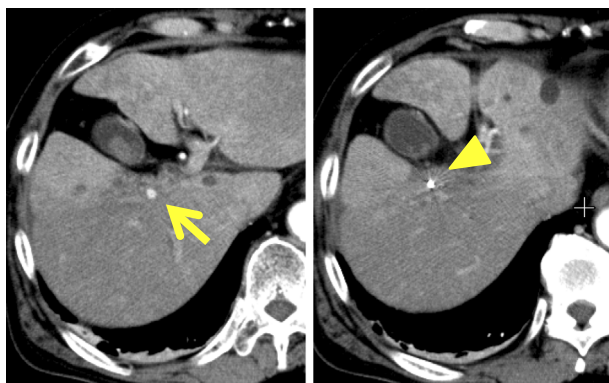
<sup>1</sup>Department of Gastroenterology, Saitama Medical Center, Jichi Medical University, Japan and <sup>2</sup>Department of Radiology, Saitama Medical Center, Jichi Medical University, Japan

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Correspondence to Dr. Takeharu Asano, takehaasano-gi@umin.ac.jp

**Table. Laboratory Data.**

WBC	9.03×10 <sup>3</sup> /μL	Alb	2.7 g/dL	BUN	25 mg/dL
Hb	9.1 g/dL	T-BIL	1.85 mg/dL	Cr	0.82 mg/dL
PLT	14.1×10 <sup>4</sup> /μL	D-BIL	1.48 mg/dL	HBsAg	(-)
PT-%	70.2 %	AST	68 IU/L	HCVAb	(+)
PT-INR	1.17	ALT	116 IU/L	HCV-RNA	undetectable
D-dimer	8.1 μg/mL	LD	272 IU/L	AFP	2 ng/mL
		ALP	429 IU/L	PIVKA-II	12 mAU/mL
		γ-GTP	123 IU/L		
		P-AMY	24 IU/L		
		CRP	18.4 mg/dL		



**Figure 1.** Contrast-enhanced computed tomography image showing a pseudoaneurysm (arrow) in the liver S5 and a hematoma in the gallbladder. The pseudoaneurysm was approximately 1 cm from the implanted fiducial marker (arrowhead) for carbon ion radiotherapy.

and abdominal pain. He underwent an abdominal computed tomography (CT), which revealed pseudoaneurysm in the anterior segment of the right hepatic artery and a hematoma in the gallbladder. He was diagnosed with bleeding into the right bile duct due to pseudoaneurysm rupture, and urgent interventional radiology treatment was needed. Thereafter, he was transferred to our hospital.

With respect to his medical history, he had been diagnosed with chronic hepatitis C at 57 years of age and successfully achieved a sustained virologic response with interferon therapy. At 74 years of age, he was diagnosed with HCC. At first, surgery was considered for HCC, but the patient wanted less-invasive treatment and was treated with carbon ion radiotherapy. Subsequently, he was followed up at the primary care hospital. There was no recurrence of HCC and no history of abdominal trauma. He had had hypertension since 76 years of age, and his blood pressure was usually regulated at approximately 140/80 mmHg (1 mmHg = 0.133 kPa) with triple therapy that included oral amlodipine 10 mg, losartan 50 mg, and hydrochlorothiazide 12.5 mg. He was not taking antiplatelet drugs or anticoagulants. He used to consume 40 g of ethanol, which he stopped after HCC treatment.

A physical examination revealed upper abdominal tenderness. His blood pressure was 133/67 mmHg, and his heart

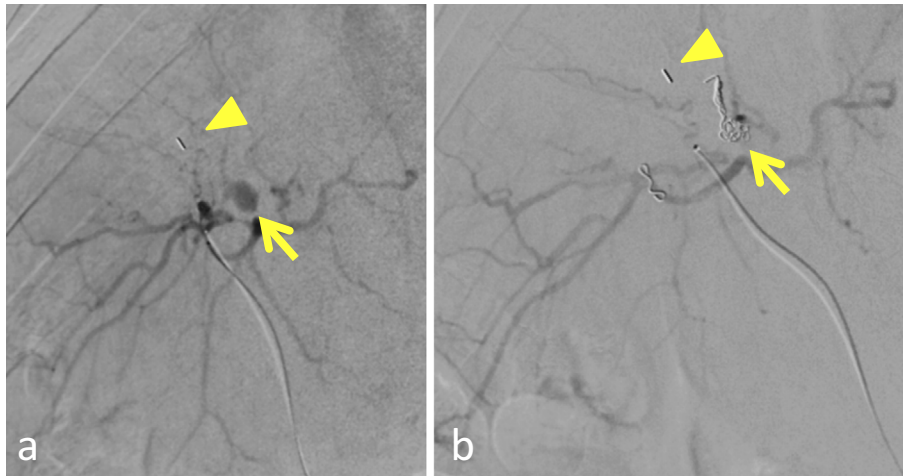
rate was 76 beats/min. Laboratory data showed a hemoglobin level of 9.1 g/dL, C-reactive protein level of 18.4 mg/dL, alpha-fetoprotein level of 2 ng/mL, protein induced by vitamin K absence or antagonist-II level of 12 mAU/mL, and an increase in hepatobiliary enzymes (Table).

On contrast-enhanced CT performed at the time of transfer, pseudoaneurysm near the radiation site of carbon ion radiotherapy in liver S5 and hematoma within the gallbladder were observed (Fig. 1). The pseudoaneurysm was approximately 1 cm from the implanted fiducial marker for carbon ion radiotherapy. There was no active HCC. Angiography revealed a hepatic pseudoaneurysm close to the fiducial marker for carbon ion radiotherapy (Fig. 2a). The patient was diagnosed with hepatic pseudoaneurysm rupture and bleeding into the intrahepatic bile duct. Embolization with coils and n-butyl-2-cyanoacrylate was performed on the pseudoaneurysm (Fig. 2b). Although his anemia did not worsen after hemostasis, he developed a fever, and the total bilirubin level rose to 3 mg/dL. Hematoma causing bile duct obstruction and cholangitis were suspected. Endoscopic retrograde cholangiopancreatography (ERCP) was performed, and a filling defect was found in the lower bile duct (Fig. 3). Hematoma release from the papilla of Vater was endoscopically confirmed. He was diagnosed with bile duct obstruction due to hematoma, for which a drainage tube was placed.

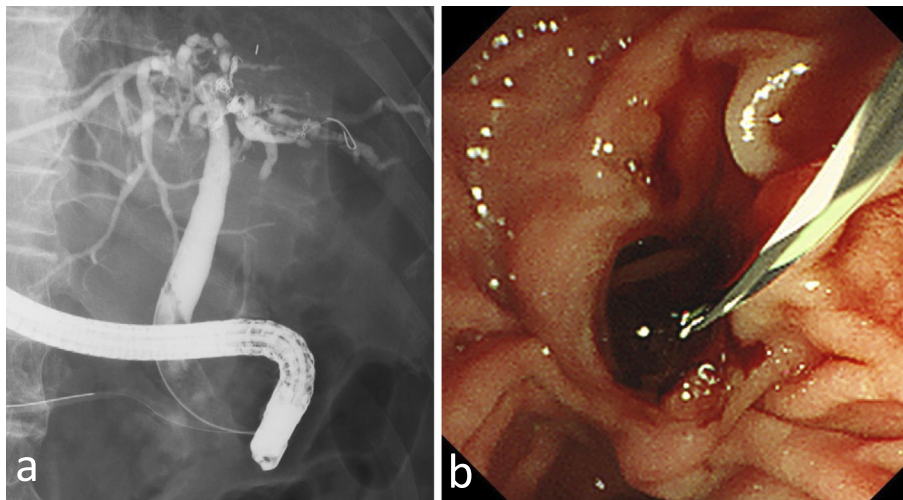
He was discharged after the completion of cholangitis treatment; however, one month later, abdominal pain recurred, and he visited the primary care hospital. Another hepatic pseudoaneurysm was suspected on contrast-enhanced CT; therefore, he was again transferred to our hospital. Another aneurysm rupture was observed near the first coil embolization site (Fig. 4a), and coil and gelatin embolization was performed (Fig. 4b). Cholangitis occurred after the second embolization, and drainage was performed using ERCP, similar to that performed for the first rupture. Subsequently, his cholangitis decreased, and he was discharged.

## Discussion

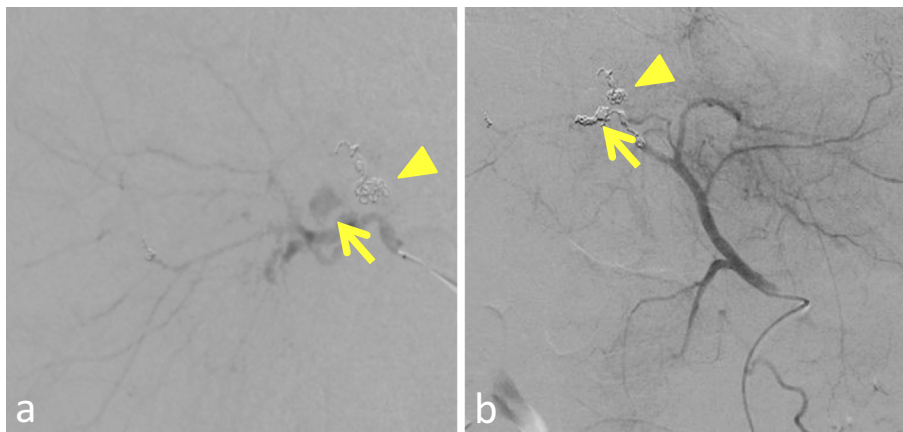
In this rare case, hepatic pseudoaneurysm ruptured into the intrahepatic bile duct nine years after carbon ion radiotherapy for HCC, and the rupture occurred twice in a short



**Figure 2.** Angiography findings at the first admission. Hepatic pseudoaneurysm (arrow) in close proximity to the implanted fiducial marker (arrowhead) for carbon ion radiotherapy (a). Pseudoaneurysm treated with coil embolization (b).



**Figure 3.** Endoscopic retrograde cholangiopancreatography showing bile duct obstruction due to hematoma. The bile duct dilatation and filling defect are visible in the lower common bile duct (a). Clot excreted from the papilla of Vater (b).



**Figure 4.** Angiography findings at the second admission. New hepatic pseudoaneurysm (arrow) in close proximity to the embolized coils in the previous treatment (arrowhead) (a). New pseudoaneurysm treated with coil embolization (b).

period of time.

The prevalence of intraabdominal aneurysm is 60% for splenic aneurysm and 20% for hepatic aneurysm (5, 6). Intrahepatic aneurysms in particular account for 20% of all cases of hepatic aneurysm. The most common cause of hepatic pseudoaneurysm is trauma, including iatrogenic trauma (7), and atraumatic causes include arteriosclerosis, inflammation, and bacterial infections. The prevalence of pseudoaneurysm rupture is as high as 90%; 43% of hepatic pseudoaneurysms burst in the peritoneal cavity and 41% in the biliary system (2). Pseudoaneurysm rupture causes anemia and hemorrhagic shock, and the mortality rate after rupture is approximately 21% (1). In the present case, hepatic pseudoaneurysm occurred at the radiation site within 1 cm of the implanted fiducial marker for carbon ion radiotherapy. Therefore, while relatively few such cases have been reported, the influence of carbon ion radiotherapy on pseudoaneurysm formation was nevertheless suspected.

Carbon ion radiotherapy has a superior dose concentration compared to conventional radiotherapy and a stronger biological effect with greater relative biological effectiveness and higher linear energy transfer than proton beam and X-ray therapy. Carbon ion radiotherapy is a new therapy that combines curability and minimal invasiveness against HCC, and the local control and overall survival rates are 81-93% and 25-36% at 5 years, respectively (8-10). Japanese clinical practice guidelines for HCC 2017 suggested that particle radiation therapy [i.e. proton radiation therapy, heavy particle (carbon ion) radiation therapy] could be considered for HCC that was difficult to treat with other local therapies (11). However, few randomized controlled trials have compared the current standard treatment for HCC against particle radiation therapy (12). This is a promising treatment for HCC patients who are elderly or have portal vein tumor thrombus or giant tumors; however, certain limitations do exist, such as the limited number of facilities that can provide particle radiation therapy and the current status of this therapy as advanced medical care. Because of its low invasiveness, it is expected that the number of patients treated with carbon ion radiotherapy for HCC will increase in the future.

Few severe adverse effects have been reported after carbon ion radiotherapy, but those mentioned include liver toxicity, hematological adverse effects, disorders of the skin and gastrointestinal tract, chest wall pain, radiation pneumonitis, and pleural effusion. The reported patient-related risk factors that cause radiation damage to normal tissues include an older age, high blood hemoglobin concentration, and smoking habit (13). Other risk factors include comorbidities, such as the effects of tumor collapse, collagen diseases, hypertension, infection, and immunosuppression. Although relatively infrequently observed as adverse effects of blood vessels due to radiotherapy, vascular stenosis and occlusion have been reported (14). Pseudoaneurysm due to radiotherapy is rare, and its mechanism remains unclear; however, it is reported to be caused by angiogenesis as well as fragmentation of the vascular mesothelial elastic fiber and

edema of the subcutaneous blood vessels due to radiation (15, 16).

In the present case, blood vessels where pseudoaneurysms occurred were present in the carbon ion radiation field and in close proximity to the implanted fiducial marker for carbon ion radiotherapy. No pseudoaneurysm had been observed on contrast-enhanced CT performed three months before the rupture, and there had been no recent trauma. Therefore, the pseudoaneurysm may have been a late adverse effect of carbon ion radiotherapy. In case reports of pseudoaneurysm rupture after radiotherapy, the period from the first radiation session to the occurrence of pseudoaneurysm was considerably large, ranging from 2.5 months to 40 years (17-21). Therefore, it is important to remember that patients with a history of radiotherapy may develop pseudoaneurysms even several years after treatment.

In the present case, there was a possibility that preceding cholangitis may have weakened the arterial wall; however, the patient had no history of recurrent cholangitis without calculus in the gallbladder, and no gallstones had been discharged in ERCP. It was also suspected that the fiducial marker implanting procedure might have contributed to the formation of the pseudoaneurysm, but the pseudoaneurysm was observed to have formed near the side of the fiducial marker instead of at the puncture site of the marker, so the influence of the marker implanting procedure was considered to be small. Anatomical abnormalities, such as vascular malformations, were not observed on CT before the rupture, and the cause of delayed pseudoaneurysm formation was unclear. However, the patient had hypertension as a comorbidity; therefore, the formation of pseudoaneurysm due to arteriosclerosis was considered. Blood pressure changes were observed during the nine years after carbon ion radiotherapy, and high blood pressure had been detected seven years before this presentation, for which the patient had started taking medication. His blood pressure was well regulated; however, the antihypertensive medication was a combination of three drugs, indicating that he had intractable hypertension and that he may have experienced transient increases in his blood pressure and pulse rate that may have exerted pressure on the blood vessel wall. Another pseudoaneurysm was formed and ruptured in a short period of one month from the first pseudoaneurysm rupture. It was considered that the fragile blood vessels in the area after the carbon ion radiotherapy might have been ruptured because of high pressure due to embolization of the first pseudoaneurysm.

In the past, treatment of pseudoaneurysms has mainly included surgical operation, aneurysmectomy, revascularization, and arterial ligation; however, in recent years, transcatheter arterial embolization has been preferred and successfully applied. Transcatheter arterial embolization is less invasive than previous employed approaches and enables the easy confirmation of vascular distribution, the position of the aneurysm, and the existence of collateral circulation. Furthermore, it is advantageous because the diagnosis and

treatment can be performed at the same time. There are risks of pseudoaneurysm rupture due to catheter manipulation inside the pseudoaneurysm and an increase in the internal pressure of the lumen as well as liver ischemia due to embolism (5); however, the success rates of transcatheter arterial embolization are reported to be 70-100% (7, 22). In the present case, considering the lesion's location at the carbon ion radiation site, the difficulty in performing surgery owing to fibrosis around the lesion, the need to review the vascular imaging of the lesion site, and the patient's advanced age, we attempted transcatheter treatment first and achieved treatment success.

Considering the extremely high rupture and mortality rates of pseudoaneurysms, early detection and proactive treatment are crucial for reducing the mortality rate of hepatic pseudoaneurysms.

### Conclusion

In this rare case, a hepatic pseudoaneurysm ruptured into the intrahepatic bile duct nine years after carbon ion radiotherapy for HCC, and the rupture occurred twice in a short period of time. Although carbon ion radiotherapy for HCC is expected to be performed increasingly frequently in the future with advances in radiotherapy, it is important to be alert for not only tumor recurrence but also the occurrence of a pseudoaneurysm during follow-up after carbon ion radiotherapy.

The authors state that they have no Conflict of Interest (COI).

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