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Brief Communication

Metal Stents for the Management of Massive Hemobilia in Patients with Hilum-Involving Cholangiocarcinoma Receiving Multi-Regimen Chemotherapy

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Recent clinical outcomes of multi-regimen chemotherapy in patients with cholangiocarcinoma (CCC) have shown benefits in terms of overall survival. However, repeated endoscopic biliary drainage (EBD) and serious adverse events negatively affect prolongation of the survival period. The aim of this study was to investigate the prevalence of massive hemobilia and the outcomes of its management with fully covered self-expandable metal stents (FC-SEMSs) in patients with hilum-involving CCC receiving multi-regimen chemotherapy. The methods and effects of FC-SEMS placement were retrospectively investigated following the occurrence of massive hemobilia during EBD. A total of 356 patients with CCC received multi-regimen chemotherapy. Among them, 181 patients had hilar invasion, and seven patients (3.9%) developed massive hemobilia during repeated EBD using removable stents. In all cases, the tumor encased the right hepatic artery. In six patients (85.7%), hemostasis was immediately and completely achieved by inserting one or two FC-SEMSs proximal to the hilar invasion area. Therefore, if the tumor encases the right hepatic artery, massive hemobilia is likely to occur during multi-regimen chemotherapy. Thus, prompt placement of a FC-SEMS would be an effective treatment option for massive hemobilia in patients with hilum-involving CCC. **(Gut Liver 2024;18:1085-1089)**

Key Words: Hemobilia; Cholangiocarcinoma; Cholangiopancreatography, endoscopic retrograde; Hilum

INTRODUCTION

Hemobilia is defined as hemorrhage within the biliary system, caused by iatrogenic injury after a hepato-biliary intervention, accidental trauma, neoplasm, and infectious or inflammatory processes.[1,2] Among the causes of hemobilia after endoscopic biliary drainage (EBD) via endoscopic retrograde cholangiopancreatography (ERCP), the placement of plastic stents or self-expandable metal stents (SEMSs) is uncommonly reported. That may be the result of stent-induced mucosal injury or the gradual erosion of an adjacent vessel, tumor, or vascular abnormality.[3-5] Malignancy itself is also a risk factor for hemobilia due to the increased vascularity and friability of the tissues involved.[6] In massive hemobilia, prompt diagnosis and definitive angiographic or endoscopic therapy should be pursued to minimize morbidity and mortality. Although catheter angiography is the standard for diagnosing and treating massive hemobilia, full-covered SEMS (FC-SEMS) insertion could be effective for emergency treatment during EBD.[7-11]

The aim of this study was to investigate the prevalence of massive hemobilia and the management outcomes of FC-SEMSs in patients with hilum-involving cholangiocarcinoma (CCC) receiving multi-regimen chemotherapy.

CASE DESCRIPTION

We reviewed consecutively enrolled patients who were diagnosed with hilum-involving CCC and treated with multi-regimen chemotherapy (gemcitabine + cisplatin ± nab-paclitaxel) between January 2020 and December 2022 at the CHA Bundang Medical Center, CHA University, Seongnam, Korea. Initial EBD was performed using more than two plastic stents. Multi-regimen chemotherapy continued until disease progression, defined according to the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1),[12] or unacceptable toxicity. Tumor response was routinely evaluated every two cycles of chemotherapy (6 weeks). In principle, scheduled EBD was performed every 2 to 3 months for stents exchange using plastic stents or removable 6 mm-sized FC-SEMSs. However, it was also performed on an emergency basis when symptoms and signs suggestive of biliary obstruction were accompanied by abnormalities in blood chemistry. This study was approved by the Institutional Review Board of CHA Bundang Medical Center (IRB number: CHAMC 2023-03-015) and performed in accordance with the ethical standards of institutional research and the Declaration of Helsinki. The requirement for informed consent was waived because the study was retrospective.

When massive hemobilia (defined as the presence of hypovolemic shock requiring resuscitation and hemodynamic stabilization)[13] was observed during stent exchange, the insertion of one or two guidewires (0.025 mm; VisiGlide 2™, Olympus Co., Tokyo, Japan) into the main intrahepatic biliary ducts (IHDs) was attempted using a cannula without delay. Then, referring to previous ERCP test findings and the Bismuth type, one or two 6 mm-sized FC-SEMSs (Hanarostent®, M.I.Tech, Pyeongtaek, Korea) of appropriate length were selected and sequentially inserted into different main IHDs (Fig. 1).

Because the effective temporizing effect for massive hemobilia from the right hepatic artery and the best drainage option for hilar obstruction, we tried to insert two FC-SEMSs into both the right IHD and left IHD. When just one guidewire was inserted into one IHD, one 6 mm-sized FC-SEMS was first inserted. Then, when the hemobilia rate decreased and an endoscopic view was secured to some extent, a cannula was inserted into the main IHD, and the insertion of a second guidewire into the other main IHD was attempted. That attempt was made to insert an additional second 6mm-sized FC-SEMS for the effective treatment of hemobilia and the best option for hilar obstruction (the add-on method) (Supplementary Fig. 1). Otherwise, when two guidewires were successfully inserted into the different main IHDs, two 6 mm-sized FC-SEMSs were simultaneously inserted into different IHDs (the simultaneous insertion method) (Supplementary Fig. 2). If hemobilia was not effectively stopped after FC-SEMS insertion or the speed

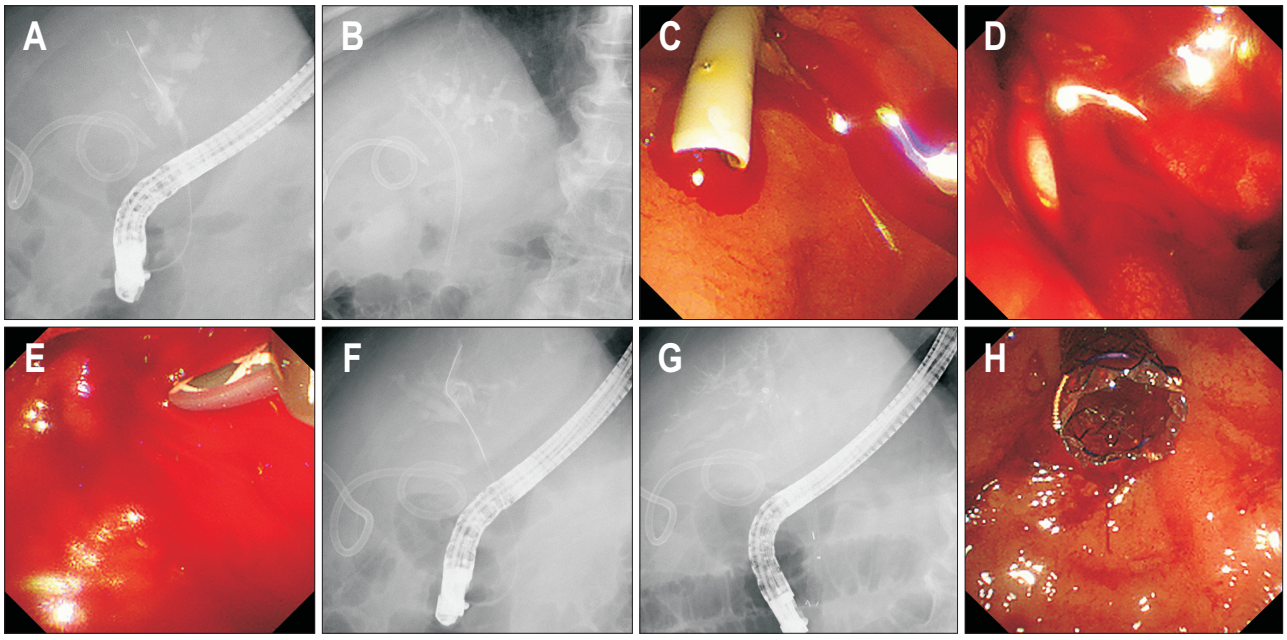

Fig. 1. Endoscopic management of hemobilia. (A, B) Previous endoscopic retrograde cholangiopancreatography examination. Hilar obstruction with marked dilation of the intrahepatic bile ducts was noted, and a plastic stent was inserted into the hilar area. (C, D) During the removal of a previously inserted plastic stent, massive hemobilia from the bile duct was observed. (E) A cannula and guidewire were blindly and successfully inserted into the site of hemobilia. (F, G) After successful insertion of a guidewire into the main intrahepatic bile duct, a 6-mm-sized fully covered self-expandable metal stent (SEMS) was inserted into the hilar area. (H) Hemobilia was successfully stopped after fully covered SEMS placement.

of hemobilia did not decrease despite FC-SEMS insertion into the right IHD, the ERCP test was stopped to perform emergent angiography without delay (Supplementary Fig. 3).

A total of 356 patients with CCC received multi-regimen chemotherapy. Among them, 181 patients had hilar invasion, and seven patients (3.9%) developed massive hemobilia while performing repeated EBDs using removable stents. Four patients had hilar CCC, two patients had intrahepatic CCC with hilar invasion, and one patient had gallbladder cancer with hilar invasion (Table 1).

In all seven cases, the tumor was encasing the right hepatic artery. The position where the right hepatic artery crossed the bile duct encased by the tumor was below the hilum in two patients and above the hilum in the other five patients. The number of previous EBD treatments varied widely from 2 to 14, and there was no significant correlation with the type and number of previously inserted plastic stents or removable FC-SEMSs, which were presumed to be the main causes of hemobilia. Regardless of tumor size changes, the distance between the bile duct and right hepatic artery at the tumor encasement area was quite short and impossible to measure before hemobilia (Supplementary Fig. 4). We tried to analyze the effect of tumor encasement and tumor size reduction on hemobilia after multi-regimen chemotherapy for the same reason, but it was not possible.

Hemostasis was primarily attempted by inserting one or two FC-SEMSs just proximally to the hilar invasion area and was immediately and completely successful in six patients (85.7%). They did not require further hemodynamic resuscitation or stabilization. In the remaining patient, hemobilia could not be stopped after one FC-SEMS insertion, since an additional guidewire insertion could not be inserted into the target area. Emergent artery embolization was performed achieving complete hemostasis. In five patients in whom two FC-SEMSs could be inserted into the target area, the simultaneous insertion method was successfully performed in four patients, and the add-on insertion method was successful in the remaining patients. Finally, hemobilia was successfully treated in all patients, but one patient died due to obstructive ileus and sepsis after 1 month. Among the patients with primary hemostasis who underwent only endoscopic treatment, elective angiography was performed after several days as an additional treatment in two patients who were expected to survive for more than 6 months, and coil embolization was performed for the complete treatment of pseudoaneurysm formation at the right hepatic artery (Table 1). All patients who underwent coil embolization were able to have FC-SEMSs exchange periodically.

Table 1. Clinical Characteristics of Hemobilia in Patients with Hilum-Involving Cholangiocarcinoma Receiving Multi-Regimen Chemotherapy

Patient No.	Sex/age (yr)	Diagnosis/bismuth type	No. of previous chemotherapy cycles	Location of RHA	No. of previous EBDs	Stent type at the last EBD	Treatment for hemobilia	Insertion method	Procedure time (sec)	Additional treatment	Prognosis
1	M/74	Hilar CCC/IIIb	6	Below hilum	2	One PS (straight-8.5 Fr-9 cm)	One FC-SEMS (6 mm–8 cm) across the papilla	Single insertion	592	Elective AE	Discharged
2	M/83	IHCCC with hilar invasion/IV	13	Above hilum	4	Two PSs (straight-7 Fr-13 cm & both pigtail-7 Fr-12 cm)	Two FC-SEMSs (6 mm–12 cm) across the papilla)	Sequential insertion	1,206	No	Discharged
3	F/58	IHCCC with hilar invasion/IIIb	9	Above hilum	4	One FC-SEMS (6 mm-10 cm) & one PS (both pigtail-7 Fr-12 cm)	Two FC-SEMSs (6 mm–12 cm) across the papilla	Sequential insertion	1,272	No	Discharged
4	F/74	Hilar CCC/IIIa	9	Above hilum	4	Three PSs (single pigtail-7 Fr-12 cm)	Two FC-SEMSs (6 mm–6 cm) above the papilla	Sequential insertion	1,504	Elective AE	Discharged
5	F/75	Hilar CCC/II	11	Above hilum	8	Two FC-SEMSs (6 mm–10 cm)	Two FC-SEMSs (6 mm–10 cm) across the papilla	Step-by-step insertion	807	No	Discharged
6	M/60	Hilar CCC/IV	15	Above hilum	14	One FC-SEMS (6 mm–10 cm) & one PS (straight-8.5 Fr-12 cm)	Two FC-SEMSs (6 mm–10 cm) across the papilla	Sequential insertion	1,839	No	Expired due to sepsis, 1 mo later
7	F/75	GB cancer with hilar invasion/IIIa	16	Below hilum	6	Two FC-SEMS (6 mm–10 cm & 6 mm–12 cm) & one PS (single pigtail-7 Fr-15 cm)	One FC-SEMS (6 mm–12 cm) across the papilla	Single insertion	603	Emergent AE	Discharged

RHA, right hepatic artery; EBD, endoscopic biliary drainage; CCC, cholangiocarcinoma; PS, plastic stent; FC-SEMS, fully covered self-expandable metal stent; AE, arterial embolization; IHCCC, intrahepatic cholangiocarcinoma; GB, gallbladder.

DISCUSSION

Herein, we first report the prevalence of massive hemobilia and the endoscopic management outcomes of FC-SEMSs in patients with hilum-involving CCC receiving multi-regimen chemotherapy. We evaluated how to successfully insert FC-SEMSs for the immediate endoscopic treatment of massive hemobilia, providing detailed examples of several cases. All patients showed the tumor encasement of the right hepatic artery and a short, non-measurable distance between the bile duct and the right hepatic artery at the tumor encasement area. This phenomenon would be a more important risk factor than the currently known hemobilia risk factors.

As shown in the results of this study, if only the guidewire could be properly positioned in the target area, the possibility of endoscopic rescue management using FC-SEMSs could be very high. Since it is accompanied by a hilar obstruction, the insertion of at least two FC-SEMSs is recommended. The insertion of two 6 mm-sized FC-SEMSs may be easier if two guidewires are inserted into both main IHDs (simultaneous insertion method). Also, we employed FC-SEMSs to encompass the right hepatic artery, with stent lengths exceeding 10 cm, using the across the papilla technique.

The causes of hemobilia were reported to be bile duct mucosal injury by stenting and the subsequent gradual erosion of an adjacent vessel, tumor, or vascular abnormality.[3-5] Recent clinical outcomes of patients with CCC receiving multi-regimen chemotherapy have shown more gains in overall survival. Thus, repeated removable stent insertion is inevitable because of the longer survival period. However, friction by the stent itself or the stent flap from repeated exchanges of removable stents may cause damage to the bile duct. Also, as mentioned earlier, in patients with hilum-involving CCC receiving chemotherapy, the most important factor is that the tumor encases the right hepatic artery and is in contact with the bile duct. Then, it is thought that damage to the gap would occur due to the following reasons: (1) when the tumor size is reduced by chemotherapy, the encasement area may be opened or become very weak; (2) during repeated stent exchange, friction by the stent itself or stent flap may cause damage to the gap; (3) even a 6 mm-sized FC-SEMS may cause pressure damage to the gap due to expansion forces; (4) repeated cholangitis inevitably occurs due to repeated chemotherapy, which could damage the gap by dormant bacterial growth; and (5) local ablation therapy or radiation therapy (no patients eligible in this study).

Although there were limitations to this study (especially, retrospective analysis and limited cases), we found that endoscopic treatment could be successfully performed if massive hemobilia abruptly occurred during ERCP and that even if it is not successful, rescue time could be obtained for additional complete treatment, such as arterial coil embolization.

In conclusion, there was a tendency for hemobilia to occur in hilum-involving CCC during multi-regimen chemotherapy when the mass encased the right hepatic artery. The prompt insertion of FC-SEMSs would be an effective option for hemobilia in patients with hilum-involving CCC receiving multi-regimen chemotherapy.

CONFLICTS OF INTEREST

H.J.C. has a consulting or advisory role at Roche, Bayer, Eisai, Ono, Bristol Myers Squibb, and Merck Sharp & Dohme. The other authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

Study concept and design: C.I.K. Data acquisition: S.Y.L., M.J.S., S.P.S., B.K. Data analysis and interpretation: C.I.K., S.Y.L., M.J.S. Drafting of the manuscript: C.I.K. Critical revision of the manuscript for important intellectual content: H.J.C., M.T. Statistical analysis: S.Y.L., M.J.S. Administrative, technical, or material support; study supervision: S.P.S., B.K., K.H.K. Approval of final manuscript: all authors.

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SUPPLEMENTARY MATERIALS

Supplementary materials can be accessed at https://doi.org/10.5009/gnl240087.

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