Successful Management of Hemosuccus Pancreaticus due to Pancreatic Adenocarcinoma by Chemoradiotherapy

Ko Tomishima¹,², Toshio Fujisawa², Sho Sato¹, Nozomi Amano¹, Ayato Murata¹, Hironori Tsuzura¹, Shunsuke Sato¹, Kouhei Matsumoto¹, Yuji Shimada¹, Ryo Wada¹, Takuya Genda¹ and Hiroyuki Isayama²

Abstract:
Management of hemosuccus pancreaticus (HP) due to pancreatic adenocarcinoma is problematic. This is the first report of the successful management of HP caused by pancreatic adenocarcinoma by chemoradiotherapy, which is a treatment option for cases with a high surgical risk that are not suitable for interventional radiology. In the present case, bloody pancreatic juice was detected in the main pancreatic duct, and anemia worsened without repeated blood transfusions. The patient ultimately underwent chemoradiotherapy comprising radiation of 3 Gy in 15 fractions concomitant with systemic chemotherapy of S-1. After the treatments, the anemia improved, and the patient was discharged on day 45.

Key words: pancreatic cancer, chemoradiotherapy, hemosuccus pancreaticus, bleeding

(Intern Med 59: 2135-2141, 2020)
(DOI: 10.2169/internalmedicine.4372-19)

Introduction
Hemosuccus pancreaticus (HP) involves bleeding from the papilla of Vater into the duodenum through the pancreatic duct. Management of HP depends on the underlying cause, and surgery or interventional radiology for selective arterial embolization is indicated in most cases. However, it is difficult to manage patients with a high surgical risk that are not suitable for interventional radiology or those with HP without vascular malformations.

We herein report a case of HP caused by pancreatic head carcinoma with multiple liver metastases treated with chemoradiotherapy (CRT). Surgery is the standard therapy for tumor-associated bleeding, but this case had unresectable metastasis. CRT may be a treatment option for patients with a high surgical risk who are unsuited for interventional radiology.

Case Report
A 67-year-old woman was admitted to our hospital complaining of epigastralgia. Her medical history included hypertension and osteoporosis, and she had no notable family medical history, smoking history, or drinking history.

She visited a nearby hospital with the chief complaint of epigastralgia, and upper gastrointestinal endoscopy revealed hemorrhaging from the papilla of Vater. Abdominal ultrasonography revealed a mass in the head of the pancreas and multiple masses in the liver. The patient was referred to our hospital for further investigation.

The presenting details were height, 146.1 cm; weight, 57.5 kg; body mass index, 26.9 kg/m²; blood pressure, 131/73 mmHg; pulse, 72 beats/min; temperature, 36.4°C; and performance status, 1. Anemia was recognized in the palpebral conjunctiva. Microcytic-hypochromic anemia and slightly elevated biliary enzyme levels were found at the first visit. In addition, there was no abnormality in the coagulation system, and the levels of tumor markers were

¹Department of Gastroenterology and Hepatology, Juntendo University Shizuoka Hospital, Japan, ²Department of Gastroenterology, Graduate School of Medicine, Juntendo University, Japan and ³Department of Pathology, Juntendo University Shizuoka Hospital, Japan
Received: December 24, 2019; Accepted: April 7, 2020; Advance Publication by J-STAGE: June 2, 2020
Correspondence to Dr. Hiroyuki Isayama, h-isayama@juntendo.ac.jp

2135
Figure 1. Intravenous contrast-enhanced computed tomography of the abdomen at the time of the diagnosis of pancreatic carcinoma (A, plain; B, arterial phase; C/D, portal phase). A low-density mass was detected in the head of the pancreas (A/B, arrowhead). Low-density masses in the liver were recognized as multiple metastases (C/D, arrow).
within the normal ranges (Table 1). Abdominal computed tomography (CT) showed a 40-mm mass lesion in the head of the pancreas. In the arterial and portal venous phases, the pancreatic head tumor was poorly enhanced and had invaded surrounding tissue. In both lobes of the liver, numerous low-density areas with ring enhancement were detected. However, aneurysm around the pancreas and extravasation in the main pancreatic duct and digestive tract were not observed (Fig. 1). An upper gastrointestinal endoscopy revealed bloody discharge from the papilla of Vater. Blood clots were detected by endoscopic retrograde pancreatography as filling defects, and bloody pancreatic juice was aspirated (Fig. 2). Endoscopic ultrasound (EUS) revealed a hypoechoic tumor with a well-defined border, 35×34 mm in size, at the head of the pancreas (Fig. 3). Subsequently, EUS-guided fine-needle aspiration was performed, and the obtained specimens were diagnosed as poorly differentiated adenocarcinoma by hematoxylin and eosin staining and based on their diffuse positivity of CK7 and p53 by immunohistochemistry (Fig. 4). Therefore, the tumor was diagnosed as stage IV pancreatic head adenocarcinoma with liver metastasis according to the Union for International Cancer Control of Pancreatic Cancer (8th edition). The cause of HP was considered pancreatic head carcinoma.

An interventional radiological approach for HP was not indicated because no aneurysm was detected by contrast-enhanced CT. Anti-tumor therapy was considered for the treatment of HP; on day 3, nab-paclitaxel plus gemcitabine therapy was started. Because tarry stool and decreased hemoglobin were observed, a 6-French nasopancreatic drainage tube was placed close to the tumor on day 14 to monitor the hemorrhaging. Bloody pancreatic juice was continuously flowing out, and blood transfusion was frequently required to prevent the anemia from worsening. Abdominal angiography was performed on day 21 because of poor control of the bleeding by stent compression, but no arterial bleeding was detected on angiography (Fig. 5). Next, radiotherapy (3 Gy in 15 fractions) was given to manage the bleeding from the pancreatic head tumor on day 22. In addition, S-1 was indicated from day 29 because CRT with nab-paclitaxel plus gemcitabine was not established at that time. On day 38 (10 days after the start of radiotherapy), the pancreatic juice from the nasopancreatic tube had become pale, and no further blood transfusion was required (Fig. 6). There were no major complications during CRT, and the patient was discharged on day 45 (Fig. 7).

Discussion

The clinical entity of HP, involving bleeding from the papilla of Vater to the duodenum through the pancreatic duct, was first described by Lower and Farrell in a report of bleeding caused by a splenic artery aneurysm in 1931 (1). Pseudoaneurysm originating from the peripancreatic vessels is a main cause of hemorrhaging involving rupture into the pancreatic duct or a pancreatic cyst connected to the pancreatic duct in the background of chronic pancreatitis. Other causes include malignancies and vascular malformations. In HP associated with pancreatic tumors, the tumors invading the pancreatic duct produce intratumoral hemorrhaging, and
tumor self-destruction causes rupture of the tumor blood vessels (2). The most common symptom is intermittent upper gastrointestinal bleeding, but epigastric pain associated with increased intraductal pressure due to clots is also reported (3). The diagnosis was confirmed by the detection of hemorrhaging from the papilla of Vater by upper gastrointestinal endoscopy. Interventional radiology and surgery are the most common treatments. As a new treatment, EUS-guided angiotherapy for bleeding pseudoaneurysm causing HP was first reported by Will et al. (4).

Figure 4. EUS-guided fine-needle aspiration histopathology showed poorly differentiated adenocarcinoma. Immunostaining revealed diffuse expression of p53 and CK7. EUS: endoscopic ultrasound

Figure 5. Celiac trunk angiography (CAG), gastroduodenal angiography (GDAG), and superior mesenteric angiography (SMAG) showed no aneurysm or extravasation.
A keyword search for ‘hemosuccus pancreaticus’ in PubMed between 1977 and 2018 yielded 161 reports. Middle-aged men with a history of alcohol abuse have multiple risk factors, and chronic pancreatitis is presumed to be an underlying disease, with pseudoaneurysm and cyst potentially occurring in the setting of inflammation. However, 10 cases of hemorrhaging from tumors, similar to the present case, were found in PubMed using the keywords ‘hemosuccus pancreaticus’ and ‘carcinoma’ (Table 2) (5-14). In particular, neoplastic HP is frequently reported in undifferentiated carcinoma, anaplastic pancreatic carcinoma, and vascular-rich tumors.

Although CRT for locally advanced pancreatic carcinoma has been reported (15-17), there are no reports of CRT as an effective treatment for hemostasis for HP due to pancreatic carcinoma. Three-dimensional conformal radiation therapy or intensity-modulated radiation therapy with a total dose of 50-54 Gy at 1.8-2 Gy per fraction is recommended for locally advanced pancreatic carcinoma (17). For gastric carcinoma, Asakura et al. reported that radiotherapy of 30 Gy in 10 fractions was efficacious and safe for preventing bleeding (18). In the present case, we chose a single dose of 3 Gy for hemostasis and applied a total of 45 Gy for local tumor control. The drainage from the nasopancreatic tube had become pale by 10 days after the initiation of RT. We consider this case to have responded to treatment, according to a retrospective cohort study of 17 cases of gastric cancer, in which hemostasis typically responded within 2 days (19).
Platelet aggregation occurs three minutes after radiotherapy, and coagulation activity is assumed to continue for seven days (20, 21). The effects of radiotherapy may support the early hemostatic response and be sustained for a re-bleeding-free survival of 27 days (19). Regarding the relationship between the tumor size and hemostasis, the tumor is not always shrunk in size on CT when the bleeding stopped because the tumor replaced post-CRT fibrosis as soft-tissue shadow on CT. Sa Cunha et al. reported that the evaluation of post-CRT re-staging on CT is inaccurate, and radical resection may be possible (22). We also temporarily controlled the tumor viability despite no effect on the tumor size. CRT may be a temporary treatment, and if the patient’s condition permits it, surgery should be chosen for the hemostasis. Pancreatic cancer sometimes shows gastrointestinal bleeding due to tumor self-destruction, for which CRT is effective.

Conclusion

We experienced a case of pancreatic ductal bleeding associated with pancreatic head carcinoma that was successfully treated by CRT. This is the first report of HP in which hemostasis was achieved by CRT. Further cases need to be gathered to determine whether or not CRT is a viable alternative treatment for cases in which surgery and interventional radiology are not feasible.

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

References

1. Lower WE, Farrell JI. Aneurysm of the splenic artery: report of a case and review of literature. Arch Surg 23: 182-190, 1931 (in Japanese).
2. Agou T, Funakoshi A, Tsubota M, et al. A case of poorly differenti-
ciated adenocarcinoma of the pancreas, noticed by massive bleeding from the papilla of vater. J Biliary Tract Pancreas 17: 857-860, 1996 (in Japanese).
3. Kouhisa J, Waguri N, Sugimura K, et al. A case of hemosuccus pancreaticus with neither aneurysms nor pseudocysts successfully treated with transcatheter arterial embolization. Endoscopic Forum for digestive disease 27: 44-49, 2011.
4. Will U, Mueller AK, Grote R, Meyer F. “Hemosuccus pancreaticus”—primarily ultrasound-guided successful intervention using transcutaneous fibrin glue application and histoacryl injection. Ultraschall Med 29 (Suppl): 260-263, 2008.
5. Kassabian A, Stein J, Jabbour N, et al. Renal cell carcinoma metastatic to the pancreas: a single-institution series and review of the literature. Urology 56: 211-215, 2000.
6. Kurland J, Matthews T, Hoff E, Gentry A, Cash B. Hemosuccus pancreaticus caused by metastatic renal cell carcinoma. Gastrointestinal Endosc 66: 1241-1242, 2007.
7. Kuruma S, Kamisawa T, Tu Y, et al. Hemosuccus pancreaticus due to intraductal papillary-mucinous carcinoma of the pancreas. Clin J Gastroenterol 2: 27-29, 2009.
8. Shinzuki M, Horii Y, Fujino Y, et al. Mucinous cystic neoplasm of the pancreas presenting with hemosuccus pancreaticus: report of a case. Surg Today 40: 470-473, 2010.
9. Inoue H, Katayama H, Hamada Y, et al. Hemosuccus pancreaticus caused by in situ carcinoma of the pancreas. Endoscopy 44: E336-E337, 2012.
10. Inoue H, Masaki K, Takei Y. Intraductal papillary mucinous neoplasm presenting as hemosuccus pancreaticus. Clin Gastroenterol Hepatol 13: e57-e58, 2015.
11. Kobayashi Y, Ito K, Inoue T, Yoneda M. Hemosuccus pancreaticus due to a tumor hemorrhaging treated with a self-expandable metallic stent in a patient with unresectable pancreatic carcinoma. Dig Liver Dis 48: 567, 2016.
12. Kawai Y, Hayashi T, Aoki M, et al. Hemosuccus pancreaticus due to pancreatic head invasive pancreatic duct carcinoma. Jpn J Cancer Chemother 45: 362-364, 2018.
13. Kanno A, Satoh K, Hamada S, et al. Serous cystic neoplasms of the whole pancreas in a patient with von Hippel-Lindau Disease. Intern Med 50: 1293-1298, 2011.
14. Mizukami Y, Arisato S, Satou K, et al. A case of anaplastic carcinoma of the pancreas, disclosed a hemosuccus pancreaticus. Nihon

Table 2. Reported Cases with the Key Words ‘hemosuccus Pancreaticus’ and ‘carcinoma’ (English Literature, 1997-2018).

| Age, Sex | Chief complaint | Kind of pancreatic disease | Location | Past history | Treatment | References |
|---|---|---|---|---|---|---|
| 1 52, M | Melena | Metastatic pancreatic tumor of RCC | Tail | - | Total pancreatectomy | 4 |
| 2 93, M | Anemia | Metastatic pancreatic tumor of RCC | Head | - | BSC | 5 |
| 3 72, F | No symptom | MD-IPMC | Head | - | PD | 6 |
| 4 71, F | Anemia | MCN | Tail | - | DP | 7 |
| 5 77, F | Dilatation of MPD | PC (Carcinoma in situ) | Head | Pancreatitis | PD | 8 |
| 6 78, M | Melena | MD-IPMN | Tail | Cerebral infarction | DP | 9 |
| 7 79, M | Anemia | PC (stage III) | Head | - | FCSEMS+GEM | 10 |
| 8 51, M | Jaundice | PC (stage III) | Head | - | PD | 11 |
| 9 35, F | Aware of tumor | Serous cystic neoplasm | Whole | Hemangioblastomas of cerebellum | Total pancreatectomy | 12 |
| 10 68, M | Melena | PC (anaplastic carcinoma) | Body, Tail | Diabetes | DP | 13 |

RCC: renal cell carcinoma, BSC: best supportive care, MD-IPMN: main-duct intraductal papillary mucinous neoplasm, PD: pancreatecoduodenectomy, MCN: mucinous cystic neoplasm, DP: distal pancreatectomy, PC: pancreas carcinoma, FCSEMS: fully covered self-expanding metal stent, GEM: gemcitabine
15. Sudo K, Yamaguchi T, Ishihara T, et al. Phase II study of oral S-1 and concurrent radiotherapy in patients with unresectable locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys 80: 119-125, 2011.

16. Shinchi H, Maemura K, Mataki Y, et al. A phase II study of oral S-1 with concurrent radiotherapy followed by chemotherapy with S-1 alone for locally advanced pancreatic cancer. J Hepatobiliary Pancreat Sci 19: 152-158, 2012.

17. Huguet F, Goodman KA, Azria D, et al. Radiotherapy technical considerations in the management of locally advanced pancreatic cancer: American-French consensus recommendations. Int J Radiat Oncol Biol Phys 83: 1355-1364, 2012.

18. Asakura H, Hashimoto T, Harada H, et al. Palliative radiotherapy for bleeding from advanced gastric cancer: is a schedule of 30 Gy in 10 fractions adequate?. J Cancer Res Clin Oncol 137: 125-130, 2011.

19. Kondoh C, Shitara K, Nomura M, et al. Efficacy of palliative radiotherapy for gastric bleeding in patients with unresectable advanced gastric cancer: a retrospective cohort study. BMC Palliat Care 14: 37, 2015.

20. Born GV. Aggregation of blood platelets by adenosine diphosphate and its reversal. Nature 194: 927-929, 1962.

21. Goldin-Lang P, Niebergall F, Antoniak S, et al. Ionizing radiation induces upregulation of cellular procoagulability and tissue factor expression in human peripheral blood mononuclear cells. Thromb Res 120: 857-864, 2007.

22. Sa Cunha A, Rault A, Laurent C, et al. Surgical resection after radiochemotherapy in patients with unresectable adenocarcinoma of the pancreas. J Am Coll Surg 201: 359-365, 2005.