Obstructive Jaundice Due to Duodenal Ulcer Induced by Lenvatinib Therapy for Hepatocellular Carcinoma

Maito Suoh, Atsushi Hagihara, Masafumi Yamamura, Hirotsugu Maruyama, Koichi Taira, Masaru Enomoto, Akihiro Tamori, Yasuhiro Fujiwara and Norifumi Kawada

Abstract:
An 82-year-old man with hepatocellular carcinoma presented with upper abdominal pain, vomiting, and jaundice. He had been taking a standard lenvatinib dose for three months. Although acute cholangitis was suggested, imaging studies failed to detect the biliary obstruction site. An endoscopic examination following discontinuation of lenvatinib and aspirin revealed multiple duodenal ulcers, one of which was formed on the ampulla of Vater and causing cholestasis. Endoscopic biliary drainage and antibiotics improved concomitant Enterobacter cloacae bacteremia. Ulcer healing was confirmed after rabeprazole was replaced with vonoprazan and misoprostol. Our case shows that lenvatinib can induce duodenal ulcers resulting in obstructive jaundice.

Key words: hepatocellular carcinoma, lenvatinib, duodenal ulcer, obstructive jaundice, aspirin

(Intern Med 60: 545-552, 2021) (DOI: 10.2169/internalmedicine.5097-20)

Introduction

Lenvatinib is a potent antiangiogenic tyrosine kinase inhibitor (TKI) that targets vascular endothelial growth factor receptor (VEGFR) 1-3, fibroblast growth factor receptor (FGFR) 1-4, platelet-derived growth factor-α, RET, and KIT (1). Based on the results of phase 3 trials focusing on radioiodine-refractory differentiated thyroid cancer (the SELECT trial) (2) and unresectable hepatocellular carcinoma (HCC) (the REFLECT trial) (3), lenvatinib is indicated as the first-line systemic therapy for these cancers (4-6). Although the prescribing information of lenvatinib warns that gastrointestinal perforation is a serious adverse reaction, the incidence of gastric or duodenal ulcer was 0.2-0.6% in those clinical trials (7). Furthermore, our literature search did not find any other publication describing upper gastrointestinal ulcer as an adverse event of lenvatinib. Thus, gastroduodenal ulcer is only rarely associated with lenvatinib therapy.

Duodenal ulcers have been sporadically complicated with obstructive jaundice (8-14). The first case in the American literature was described in 1853 (8) and similar reports have been published since then (9-14). When inflammation of the duodenal ulcer extends to the surrounding structures, including the ampulla of Vater, pancreas, and hepatoduodenal ligament, it can lead to external compression of the biliary tract and subsequent cholestasis (8, 9). Under these conditions, obstructive jaundice results from not only peptic ulcer (8, 9, 11) but also duodenal injuries associated with medical procedures, such as endoscopic hemostasis for bleeding ulcer (10, 12), percutaneous endoscopic gastrosomy (13), and transarterial radioembolization for HCC (14). Nevertheless, this condition has never been reported as a complication of systemic therapy.

Using the radiological criteria of modified RECIST (mRECIST) (15), the REFLECT trial showed that lenvatinib led to more favorable progression-free survival and objective response rate than sorafenib (3), another first-line multitargeted antiangiogenic TKI for HCC (5, 6). RECIST version 1.1 is used to assess the size of solid tumors in general (16), whereas mRECIST is specifically designed for HCC to evaluate intratumoral arterial enhancement on contrast-enhanced computed tomography (CT) or magnetic resonance imaging under the assumption that it reflects tu
Figure 1. Contrast-enhanced computed tomography before initiating lenvatinib. An ill-defined heterogeneous arterial phase hyperenhancement (A) and washout on portal phase (B) in the right lobe of the liver indicated hepatocellular carcinoma. The inferior side of the hypervascular tumor invaded the main right portal vein (C), which was depicted as a perfusion defect on portal phase (D) (arrow).

Case Report

An 82-year-old man with HCC presented with upper abdominal pain and vomiting. He had achieved hepatitis C virus eradication with sofosbuvir and ledipasvir two years previously, but the background liver was cirrhotic. Despite two courses of transcatheter arterial chemoembolization followed by local ablation during the previous year, the patient developed recurrence of HCC. The tumor in the right lobe exhibited ill-defined heterogeneous arterial phase hyperenhancement (Fig. 1A) and washout on portal phase (Fig. 1B). The inferior side of the lesion had invaded the main right portal vein (Fig. 1C, D). The baseline serum levels of α-fetoprotein and des-γ-carboxy prothrombin were markedly elevated to 9,276 ng/mL (normal range 0-20 ng/mL) and 7,619 mAU/mL (normal range 0-39 mAU/mL), respectively.

He had been continuously receiving a standard dose of lenvatinib (8 mg/day based on body weight of 59 kg) without any adverse events for 3 months.

His medical history included coronary stent placement for angina pectoris performed three years previously. He was taking low-dose aspirin as antiplatelet therapy, in addition to rabeprazole and several oral medications for hypertension, type 2 diabetes mellitus, and dyslipidemia. The results of routine esophagogastroduodenoscopy conducted one month before introducing lenvatinib were normal except for a small esophageal varix and mild chronic gastritis.

On admission, the patient complained of abdominal discomfort in the epigastrium and right upper quadrant. The vital signs were notable for a low-grade fever (37.5 °C) and hypertension (184/94 mmHg). A physical examination revealed mild icterus but otherwise unremarkable findings, including in the abdomen. Laboratory tests were significant for increases in the white blood cell count (13,600/μL) and serum levels of total bilirubin (5.0 mg/dL), direct bilirubin (3.3 mg/dL), aspartate aminotransferase (278 U/L), alanine aminotransferase (125 U/L), alkaline phosphatase (654 U/L), γ-glutamyl transpeptidase (332 U/L), and C-reactive protein (2.68 mg/dL).

Contrast-enhanced CT revealed dilatation of the common bile duct (Fig. 2A, B). There was no wall thickening of the small or large intestine that suggested intestinal inflamma-
Although the findings on admission suggested acute cholangitis (17), imaging studies were unable to determine the cause of biliary obstruction. After discontinuing lenvatinib and aspirin, we performed endoscopic retrograde cholangiopancreatography (ERCP). The endoscopic examination revealed multiple ulcers in the bulb and descending portion of the duodenum (Fig. 4A-C), whereas no mucosal damage was observed in the stomach. Remarkably, one of the duodenal ulcers had formed on the swollen ampulla of Vater, from which infective bile was leaking (Fig. 4C). Cholangi-
Figure 4. Endoscopic retrograde cholangiopancreatography after admission. An endoscopic examination revealed multiple ulcers in the bulb and descending portion of the duodenum (A-C). One of the duodenal ulcers formed on the swollen ampulla of Vater, from which infective bile was leaking (C). Cholangiography revealed several inhomogeneous unfilled areas, compatible with pus accumulation, in the common bile duct without stricture (D). Endoscopic sphincterotomy (E) and balloon sweeping of the common bile duct (F) were subsequently performed.

Biliary drainage by endoscopic sphincterotomy (EST) (Fig. 4E) and balloon sweeping (Fig. 4F). A biopsy of the duodenal ulcers was not obtained due to the prescribing information of lenvatinib warning about delayed wound healing (7).

Blood and bile cultures identified Enterobacter cloacae bacteremia, which improved with the biliary drainage and administration of cefepime and metronidazole. The patient’s serum Helicobacter pylori antibody was negative. For the treatment of duodenal ulcers, rabeprazole was replaced with vonoprazan in combination with the temporal use of misoprostol. Duodenoscopy performed 12 days after ERCP confirmed healing of the ulcers (Fig. 5A, B), and antiplatelet therapy was resumed with clopidogrel rather than aspirin.

To determine the objective response of HCC and thereby assess the benefit of resuming lenvatinib despite the serious consequence of duodenal ulcers, we performed contrast-enhanced CT again on admission day 17. In contrast to the results on admission (Fig. 2C, D), the HCC lesion exhibited restored arterial enhancement (Fig. 6A). Although the increase in tumor size did not meet the threshold for progressive disease according to RECIST version 1.1 (Fig. 6B) (16), the confirmation of aggravating tumor burden resulted in the termination of lenvatinib therapy.

Discussion

In this report, lenvatinib therapy induced a sequence of unusual conditions, namely duodenal ulcers and resulting obstructive jaundice, in a patient with HCC taking aspirin. We carefully adapted the treatment to this unique adverse event and incidentally observed radiological changes in HCC that provided insight into how to assess the treatment response to lenvatinib.

Gastrointestinal ulceration and eventual perforation are possible adverse events of antiangiogenic therapies, including monoclonal antibodies (18-24) and TKIs (25, 26), although the reported incidences are generally less than 2% in large-scale studies (18-26). The risk factors for gastrointestinal perforation are well-investigated in studies of bevacizumab, a monoclonal antibody against VEGF (18-23). One risk factor is the presence of a tumor in the gastrointestinal tract (18, 21-23), which can become necrotic following the chemotherapy. This finding is consistent with reports describing perforated intestinal metastasis of thyroid cancer.
(27) and HCC (28) during lenvatinib therapy. However, the duodenal ulcerations in our patient appeared and healed with the initiation and discontinuation of lenvatinib, respectively, suggesting a causal relationship to the treatment but a benign nature of these lesions.

Concomitant non-steroidal anti-inflammatory drugs (NSAIDs) during antiangiogenic therapy can also predispose patients to gastrointestinal perforation, as shown in a post-marketing study of bevacizumab in Japanese patients with colorectal cancer (23). In our patient, however, aspirin, which itself is a risk factor for gastroduodenal mucosal damage (29, 30), was unlikely to be the primary cause of the duodenal ulcers because these lesions had been absent despite the regular intake of the drug. Notably, because anti-platelet therapy was prohibited in the REFLECT trial (31) and no other study has addressed this issue, the safety profile of lenvatinib has not been established in patients with HCC who are taking aspirin. Hence, our report also provides safety information on the combined use of lenvatinib and aspirin.

Pharmacological perturbation of multiple molecular pathways may have contributed to the duodenal ulcers in our patient. In a rat study, lenvatinib caused chronic duodenal inflammation initiated upon damage to the Brunner’s gland, and the authors attributed this phenomenon to disrupted VEGF signaling (32). Furthermore, blockade of the VEGF-VEGFR system reduced the intestinal blood flow by decreasing the number of intestinal capillaries in mouse models (18, 33, 34). Although one study reported that this reduction was insufficient to impair the intestinal function (18, 33), further mucosal damage may have been induced by inhibiting other target pathways of lenvatinib, particularly fibroblast growth factor (FGF) signaling. FGFR1-4 are differentially expressed in each layer of the duodenal wall and microvessels (35). In addition to proangiogenesis (36), the FGF-FGFR system plays various physiological roles in the adult intestine, such as promoting the proliferation and differentiation of intestinal cells, maintaining intestinal stem cell homeostasis, and triggering tissue repair (37). Furthermore, aspirin is classically known to exert damaging effects on the gastroduodenal mucosa through cyclooxygenase inhibition (29, 30). Thus, the net result of molecular suppression by lenvatinib and aspirin is speculated to be involved in the development of duodenal ulcers.
The endoscopic features of duodenal ulcers related to antiangiogenic agents have been described only in a few case reports (38–42). This may be because duodenal injury with these chemotherapeutic regimens is not only rare but also likely to manifest as perforation and require emergent management, such as surgery (22). Typically, peptic duodenal ulcers, including those induced by aspirin or NSAIDs, are either single or multiple lesions located in the duodenal bulb (29). Indeed, previous reports described deep and often penetrating ulcers in the bulb caused by bevacizumab (38, 40, 41) or pazopanib, a multiple TKI indicated for renal cell carcinoma and malignant soft tissue tumor (42). However, compared with these cases, the endoscopic findings of our patient differed in that the ulcers were rather superficial and extended to the descending portion, including the ampulla of Vater. Of note, similar multiple ulcers in the descending portion, but sparing the major duodenal papilla, were reported in a case of HCC treated with sorafenib (39). Therefore, despite the limited and inconsistent information available at present, we can speculate that duodenal mucosal damage affecting the descending portion may be associated with multitargeted antiangiogenic TKIs.

The treatment strategy for obstructive jaundice secondary to duodenal ulcer should be determined based on each particular situation. Successful endoscopic biliary drainage has been reported in this setting (13, 14), whereas surgical intervention was selected in older studies (8, 9) or for cases suspected of having malignant biliary obstruction (11, 12). In our patient, an endoscopic examination was the first-choice approach for identifying the cause of cholestasis, and bacteremia resulting from cholangitis necessitated urgent biliary drainage (43). The rationale for selecting EST is to resolve biliary obstruction caused by edematous papilla and promptly remove pus from the common bile by balloon sweeping. While endoscopic biliary stenting and nasobiliary drainage would have been safer than EST, these approaches are associated with risks of tube obstruction or displacement (44). Although endoscopic treatment can be completed in a single procedure via EST without stent insertion (44), potential serious complications include bleeding and perforation (45). While EST under aspirin monotherapy is acceptable in patients at a high risk of thromboembolism (45, 46), perforation was a concern in the present study because of the incision to the ulcer and delayed wound healing related to lenvatinib (7). Therefore, in addition to the withdrawal of lenvatinib and aspirin, we modified the antiulcer medications to facilitate the recovery of duodenal ulcers and EST incision. Both vonoprazan (potassium-competitive acid blocker) (47) and misoprostol (prostaglandin E1 analogue) (48) are effective for treating aspirin-induced gastroduodenal ulcer via different mechanisms of action. As the ulcers healed successfully, our case suggests that a transpapillary endoscopic procedure is feasible for managing obstructive jaundice caused by an ampullary ulcer when combined with appropriate antiulcer therapy.

The radiological changes of HCC in our patient represent a pitfall in the interpretation of the treatment response during lenvatinib therapy. The tumor exhibited paradoxical CT findings during lenvatinib therapy, showing an increase in size but a lack of arterial enhancement. The rapid recovery of intratumoral perfusion suggested that the remaining hypodense lesion was still a viable tumor, not necrotic tissue. This, in turn, implies that arterial enhancement does not always correlate with tumor viability during lenvatinib therapy. It should be emphasized that our patient received the maximal dose intensity of lenvatinib until the initial radiological assessment, while a reduced relative dose intensity can negatively affect the objective response of HCC (49, 50). Therefore, it is essential to clarify whether or not the objective response of HCC based on mRECIST during lenvatinib therapy has a meaningful impact on the clinical outcomes, particularly the prognosis. Real-world studies have shown that patients with HCC who had a favorable response to lenvatinib based on mRECIST achieved a better overall survival than those who did not (50, 51).

In conclusion, we encountered a case of obstructive jaundice due to duodenal ulcer induced by lenvatinib therapy for HCC. The endoscopic features are characterized by multiple ulcerations in the bulb and descending portion of the duodenum, including the ampulla of Vater. The pathogenesis of the duodenal ulcers may be attributable to the inhibition of various molecular pathways by lenvatinib and aspirin. Prompt endoscopic treatment and antiulcer therapy were successful in managing this case of cholangitis with bacteremia. Further research is warranted to investigate the role of an objective response to lenvatinib therapy in patients with HCC.

The patient provided his written informed consent for publication of this article and the accompanying images.

Author’s disclosure of potential Conflicts of Interest (COI). Yasuhiro Fujiwara: Honoraria, EA Pharma and Takeda. Norifumi Kawada: Honoraria, Gilead Sciences and MSD; Research funding, Gilead Sciences.

References

1. Yamamoto Y, Matsui J, Matsushima T, et al. Lenvatinib, an angio-
genesis inhibitor targeting VEGFR/FGFR, shows broad antitumor activity in human tumor xenograft models associated with microvessel density and pericyte coverage. Vasc Cell 6: 18, 2014.
2. Schlumberger M, Tahara M, Wirth LJ, et al. Lenvatinib versus pla-
cebo in radioiodine-refractory thyroid cancer. N Engl J Med 372: 621–630, 2015.
3. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular car-
cinoma: a randomised phase 3 non-inferiority trial. Lancet 391: 1163–1173, 2018.
24. Wang Z, Durante C, Hartl D, et al. Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 30: 1856-1883, 2019.

25. Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. Hepatology 68: 723-750, 2018.

26. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatocellular carcinoma. J Hepatol 69: 182-236, 2018.

27. Tran B, Dunning K, Kohli H. QUIZ HQ 55. Unusual cause of obstructive jaundice. Ann Intern Med 142: 1001-1010, 1995.

28. Dagradi AE, Schindler R. Pancreatic insufficiency and obstructive jaundice due to chronic duodenal ulcer: a case report. Am J Gastroenterol 32: 708-713, 1959.

29. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment of tumor response in hepatocellular carcinoma. Eur J Cancer 45: 228-247, 2009.

30. Ishihara Y, Shirao K. Gastrointestinal ulceration as a possible complication of sclerosant injection for bleeding duodenal ulcer. Gut 35: 1665-1667, 1994.

31. Ho CY, Chen TS, Chang FY, Lee SD. Benign nontraumatic inflammatory stricture of duodenum as a complication of sclerosant injection for bleeding duodenal ulcer. World J Gastroenterol 10: 75-92, 2010.

32. Crismale JF, Ward SC, Ahmad J. An unusual cause of abdominal pain and biliary obstruction as a complication of a peptic duodenal ulcer mimicking pancreatic cancer. Endoscopy 42 (Suppl 2): E294-E295, 2010.

33. Tran B, Dunning K, Kohli H. QUIZ HQ 55. Unusual cause of obstructive jaundice and cholangitis. J Gastrointestin Liver Dis 19: 75-92, 2010.

34. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment of tumor response in hepatocellular carcinoma. Semin Liver Dis 30: 52-60, 2010.

35. Ishihara Y, Shirao K. Gastrointestinal ulceration as a possible complication of sclerosant injection for bleeding duodenal ulcer. Gut 35: 1665-1667, 1994.

36. Ho CY, Chen TS, Chang FY, Lee SD. Benign nontraumatic inflammatory stricture of duodenum as a complication of sclerosant injection for bleeding duodenal ulcer. World J Gastroenterol 10: 75-92, 2010.

37. Hidalgo L, Repiso A, Romero M, et al. Obstructive jaundice as a complication of a peptic duodenal ulcer mimicking pancreatic cancer. Endoscopy 42 (Suppl 2): E294-E295, 2010.

38. Tran B, Dunning K, Kohli H. QUIZ HQ 55. Unusual cause of obstructive jaundice and cholangitis. J Gastrointestin Liver Dis 19: 75-92, 2010.

39. Hughes SE. Differential expression of the fibroblast growth factor receptor (FGFR) multigene family in normal human adult tissues. J Histochem Cytochem 45: 1005-1019, 1997.

40. Tomishige H, Hashizume H, et al. VEGF-dependent plasticity of fenestrated capillaries in the normal adult microvasculature. Am J Physiol Heart Circ Physiol 290: H560-H576, 2006.

41. Yang Y, Zhang Y, Cao Z, et al. Anti-VEGF- and anti-VEGF receptor-induced vascular alteration in mouse healthy tissues. J Pathol 246: 344-352, 2017.

42. Fukushima K, Terakura M, Katsuragi K. Severe gastric and duodenal injury associated with long-term low-dose aspirin therapy. World J Gastroenterol 19: 1673-1682, 2013.

43. Ishihara Y, Shirao K. Gastrointestinal ulceration as a possible complication of sclerosant injection for bleeding duodenal ulcer. Gut 35: 1665-1667, 1994.

44. Ho CY, Chen TS, Chang FY, Lee SD. Benign nontraumatic inflammatory stricture of duodenum as a complication of sclerosant injection for bleeding duodenal ulcer. World J Gastroenterol 10: 75-92, 2010.

45. Hughes SE. Differential expression of the fibroblast growth factor receptor (FGFR) multigene family in normal human adult tissues. J Histochem Cytochem 45: 1005-1019, 1997.

46. Tomishige H, Hashizume H, et al. VEGF-dependent plasticity of fenestrated capillaries in the normal adult microvasculature. Am J Physiol Heart Circ Physiol 290: H560-H576, 2006.

47. Yang Y, Zhang Y, Cao Z, et al. Anti-VEGF- and anti-VEGF receptor-induced vascular alteration in mouse healthy tissues. J Pathol 246: 344-352, 2017.
45. Ryozawa S, Itoi T, Katanuma A, et al. Japan Gastroenterological Endoscopy Society guidelines for endoscopic sphincterotomy. Dig Endosc 30: 149-173, 2018.
46. Fujimoto K, Fujishiro M, Kato M, et al. Guidelines for gastrointestinal endoscopy in patients undergoing antithrombotic treatment. Dig Endosc 26: 1-14, 2014.
47. Kawai T, Oda K, Funao N, et al. Vonoprazan prevents low-dose aspirin-associated ulcer recurrence: randomised phase 3 study. Gut 67: 1033-1041, 2018.
48. Donnelly MT, Goddard AF, Filipowicz B, Morant SV, Shield MJ, Hawkey CJ. Low-dose misoprostol for the prevention of low-dose aspirin-induced gastroduodenal injury. Aliment Pharmacol Ther 14: 529-534, 2000.
49. Takahashi A, Moriguchi M, Seko Y, et al. Impact of relative dose intensity of early-phase lenvatinib treatment on therapeutic response in hepatocellular carcinoma. Anticancer Res 39: 5149-5156, 2019.
50. Kuzuya T, Ishigami M, Ito T, et al. Favorable radiological antitumor response at 2 weeks after starting lenvatinib for patients with advanced hepatocellular carcinoma. Hepatol Res 50: 374-381, 2020.
51. Kaneko S, Tsuchiya K, Kurosaki M, et al. Three criteria for radiological response on survival in patients with hepatocellular carcinoma treated with lenvatinib. Hepatol Res 50: 137-143, 2020.