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CASE REPORT

Severe gastrointestinal hemorrhage related to everolimus: a case report

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Abstract
Everolimus is an mTOR (the mammalian target of rapamycin) inhibitor, which is used for the treatment of advanced renal cell carcinoma. Life-threatening hemorrhages are extremely rare adverse effect of everolimus. We herein report a successfully treated case of severe everolimus-related gastrointestinal hemorrhage by emergency surgical resection for patient with advanced renal cell carcinoma. A 72-year-old male was diagnosed with renal cell carcinoma, for which everolimus was administered after unsuccessful treatment with sunitinib and sorafenib. The patient suddenly developed hematemesis 4 weeks after administration. Upper gastrointestinal endoscopy showed gastric antral vascular ectasia. Once the hemorrhage was successfully cauterized by argon plasma coagulation, everolimus was discontinued. However, the patient after re-administration of everolimus developed hematemesis again and exhibited hemorrhage shock. Since therapeutic endoscopy could not achieve hemostasis, the patient underwent emergency distal gastrectomy with Billroth I reconstruction. The patient's vital signs and hemoglobin level stabilized after the surgery. Thereafter, the patient made a satisfactory recovery, and was discharged on postoperative day 10.

Keywords Everolimus · mTOR inhibitors · Gastrointestinal hemorrhage

Background

The introduction of targeted agents has improved the prognosis of several types of cancer, including renal cell carcinoma. On March 30, 2009, the U.S. Food and Drug Administration approved everolimus, an mTOR (the mammalian target of rapamycin) inhibitor, as the second-line treatment of advanced renal cell carcinoma after failure of sunitinib or sorafenib. Commonly reported adverse effects of everolimus include stomatitis, rash, fatigue, asthenia and diarrhea [1]. Minor hemorrhage is relatively common, while life-threatening hemorrhage has seldom been reported. We herein report a successfully treated case of severe everolimus-related gastrointestinal hemorrhage by emergency surgical resection for patient with advanced renal cell carcinoma.

Case presentation

A 72-year-old male who had been diagnosed with an advanced renal cell carcinoma with lung, liver, bone and lymph node metastases (T3aN0M1, according to Japanese

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classification system, the 4th edition) 15 month earlier, was admitted to our hospital for evaluation and treatment of hematemesis. The patient had mild anemia but no past medical history of gastrointestinal disease. The patients had undergone right nephrectomy and received targeted therapy with sunitinib. After four months, sunitinib was switched to axitinib because of neutropenia. Six months later, axitinib was switched to everolimus (5 mg/day) because of slight progression of the multiple metastatic lesions (liver, lung, lymph node and bone). When the patient had started treatment with everolimus, upper gastrointestinal endoscopy showed only atrophic gastritis (Fig. 1a), and rapid urease test showed no evidence of *Helicobacter pylori* infection. Four weeks after starting everolimus, the patient suddenly developed hematemesis.

On initial examination, the patient's vital signs were stable. Complete blood count revealed the hemoglobin level remarkably decreased from 9.9 to 4.5 g/dl in one month. He was transfused four units of red blood cell concentrate (RCC). Emergency upper gastrointestinal endoscopy showed diffuse oozing in the antrum, which was similar to gastric antral vascular ectasia (GAVE) (Fig. 1b), for which hemostasis was achieved by repeated argon plasma coagulation (APC), proton pump inhibitor and by discontinuing everolimus.

Since everolimus was not suspected as the cause of bleeding, everolimus was restarted. One week later, the hemoglobin level gradually decreased and the patient finally developed hematemesis again. We cancelled the administration of everolimus. Emergency upper gastrointestinal endoscopy showed diffuse antral oozing and mucosal denudation. Despite APC and band ligation, bleeding could not be controlled (Fig. 1c), which resulted in hemorrhagic shock. Two weeks after restarting everolimus, the patient, therefore, underwent emergency distal gastrectomy with Billroth I reconstruction. The patient's vital sign and hemoglobin level stabilized after the surgery. Thereafter, the patient made a satisfactory recovery, and was discharged on postoperative day 10. Overall, during the 30-day period of treatment for the hemorrhage, we performed a total of 6 sessions of therapeutic endoscopy and administered 40 units of packed red blood cell.

The resected specimens revealed mucosal necrosis in the antrum (Fig. 2a). The necrotic changes were localized to the mucosa and the lesion was well-defined. Pathological examination showed that fibromuscular proliferation, capillary fibrin thrombosis and vascular congestion within the mucosal and submucosal layer around the lesion (Fig. 2b). In addition, atrophic changes were observed in the duodenal mucosa. These findings were compatible with the GAVE. Interferon-alpha was administered as fourth-line

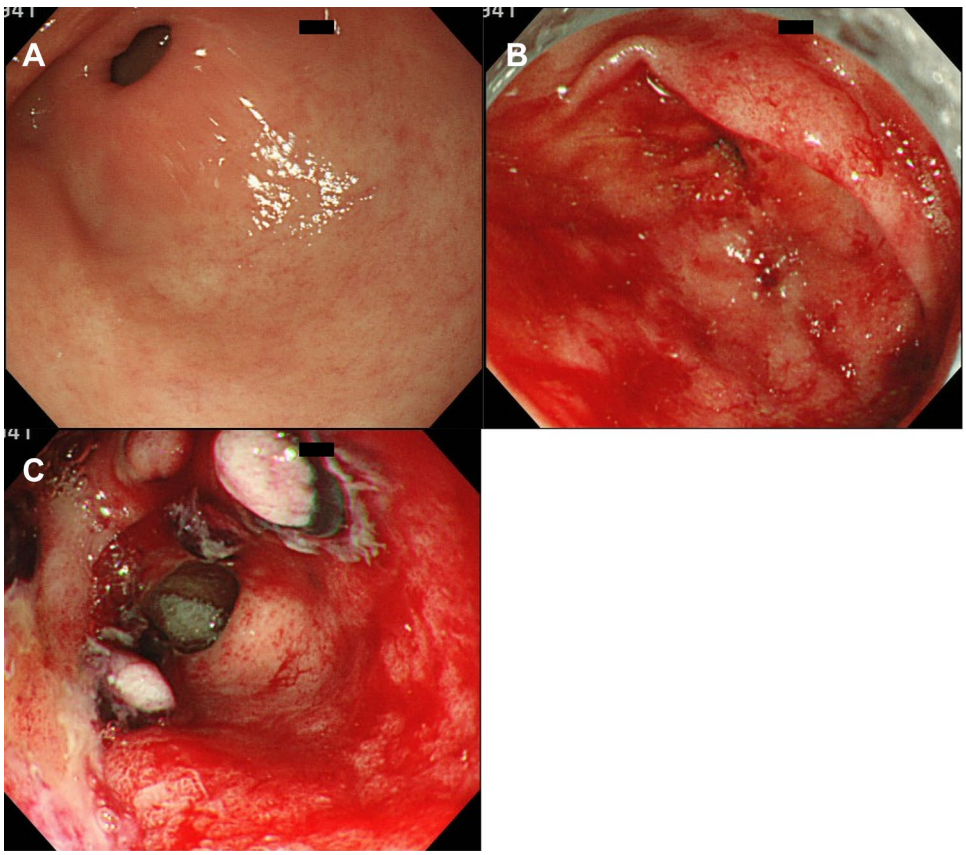

Fig. 1 Upper gastrointestinal endoscopy. **a** Atrophic gastritis before administration of everolimus. **b** Diffuse antral oozing and mucosal denudation after 4 weeks from administration of everolimus. **c** APC and band ligation could not achieve hematemesis

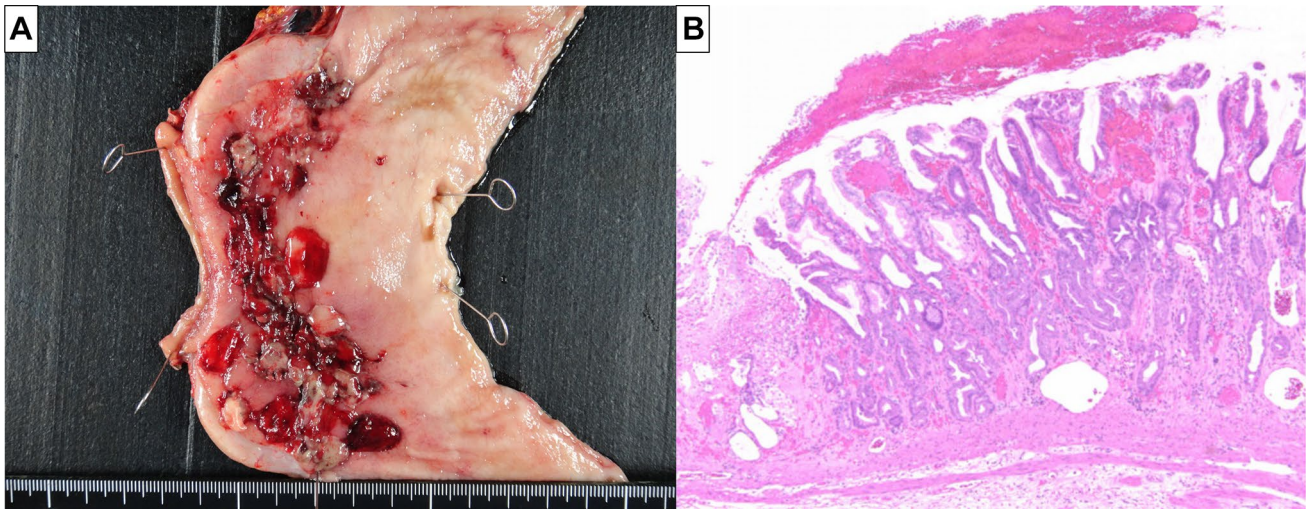

Fig. 2 The resected specimen and pathological examination. **a** The resected specimens revealed mucosal necrosis in the antrum. **b** Pathological examination showed fibromuscular proliferation within the lamina propria with capillary fibrin thrombosis

chemotherapy, and the patient remains well without any gastrointestinal symptoms as of 3 months after surgery.

Discussion

Life-threatening hemorrhages are extremely rare adverse effect of everolimus. As to severe gastrointestinal hemorrhage due to everolimus, two case reports have been published in the English literature; details of present case and other 2 cases are summarized in Table 1 [2, 3]. Two of the three patients developed GAVE, and the other patient developed erosive gastritis. All the patients developed hemorrhage one month later after administration. In the present case, since the patient had none of the comorbidities associated with GAVE and no evidence of GAVE on upper gastrointestinal endoscopy prior to the treatment with everolimus, the bleeding was not initially suspected as caused by everolimus.

The mechanism by which everolimus caused gastrointestinal hemorrhage is unclear. Temsirolimus, another type of mTOR inhibitors on the other hand has been reported to cause GAVE [4, 5]. These case reports suggest there are some relationships between mTOR inhibitors and gastrointestinal hemorrhage. The activation of mTOR signaling pathways promote wound healing in the stomach [6]. Thus, the mTOR inhibitors may prevent mucosal healing in the stomach and trigger gastritis and gastrointestinal bleeding.

For gastrointestinal hemorrhage due to GAVE, most case have successfully been cauterized using APC, upon attempting numerous sessions of therapeutic endoscopy and

Table 1 Cases of life-threatening gastrointestinal hemorrhage due to everolimus

First author	Current case	Gonzales P	Assi H
Year	2016	2017	2014
Sex	Male	Female	Female
Age (years)	72	60	48
Type of carcinoma	Renal cell carcinoma	Breast cancer	Breast carcinoma
Duration from starting everolimus to hemorrhage	1 month	1 month	1 month
Endoscopic findings	Diffuse antral oozing	Multiple flat erosions with blood oozing	Diffuse antral oozing
Endoscopic diagnosis	GAVE	Erosive gastritis	GAVE
Treatment given	APC, band ligation, distal gastrectomy	APC	APC
Sessions of EGD	6	Multiple	13
Units of packed red blood cell given	40	13	52
Postoperative course	Alive, 1 month	Alive, at least 1 week	Alive, 1 month

EGD esophagogastroduodenoscopy, *GAVE* gastric antral vascular ectasia, *APC* argon plasma coagulation

transfusion of large amounts of RCC [7, 8]. Surgical treatment for GAVE has rarely been reported [9]. In the present case, it was important to remove the bleeding source because treatments only for mucosa were insufficient to control bleeding. It was worth noting that everolimus was resumed in all three cases and bleeding occurred again. Knowledge of potentially life-threatening adverse effects is of great importance to empower the caring physician to discontinue therapy when these events are recognized. The present case seems informative because upper gastrointestinal endoscopy before administration of everolimus was unremarkable and rapid changes in the antrum of the stomach were confirmed after the administration of everolimus.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human and animal rights All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008(5).

Informed consent The patient has given consent for the publication of images.

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