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CASE REPORT

LIFE-THREATENING EVEROLIMUS-ASSOCIATED EROSIVE-HEMORRHAGIC GASTROPATHY IN A LIVER TRANSPLANT PATIENT

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Summary

We present the case of a patient who, following liver transplantation and optimization of the immunosuppressive regimen consisting of everolimus in combination with tacrolimus, presented several episodes of gastrointestinal bleeding, with endoscopic evidence of erosive hemorrhagic gastropathy. Modification of immunosuppression led to resolution of gastropathy and of bleeding events. Rare cases of life-threatening digestive hemorrhage due to everolimus have been reported in the literature, including a single case of hemorrhagic gastropathy. Given the widespread use of mammalian target of rapamycin inhibitors as part of chemotherapy or immunosuppressive protocols it is important to document this rare but potentially life-threatening side effect.

Key words: transplantation, immunosuppression, gastrointestinal bleeding, argon plasma coagulation

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INTRODUCTION

Liver transplantation (LT) is a potential treatment for end-stage liver failure and hepatocellular carcinoma [1,2]. Over the years, immunosuppressive regimens for patients receiving LT have been revised to enhance both graft and patient survival. Everolimus, a mammalian target of rapamycin (m-TOR) inhibitor, is approved as immunosuppressive targeted therapy in combination with calcineurin inhibitors such as tacrolimus or corticosteroids in patients undergoing LT, with the aim to prevent allograft rejection preserving the immune control over neoplasia and infections [3]. The most common adverse effects of everolimus include stomatitis, diarrhea, asthenia, rash, fatigue, vomiting and dry mouth, while gastrointestinal bleeding is not reported among them [4,5]. Very few cases of gastrointestinal (GI) bleeding associated with use of everolimus during chemotherapy consisting in mTOR inhibitors have been documented in the literature, and only one case in a LT patient was reported after two years of everolimus and concomitant introduction of apixaban [6-10].

CASE REPORT

A 76 year-old gentleman underwent LT in March 2022 for multifocal

hepatocellular carcinoma. Patient's history included portal hypertension characterized by a single episode of minimal ascites in 2017, and the presence of phlebectasias of the lower esophagus without previous episodes of GI bleeding.

Single-agent immunosuppression with tacrolimus was the initial immunosuppressive regimen, with the combination of everolimus (1.25 mg/daily) following in May 2022, while prophylactic acetylsalicylic acid (ASA) with proton pump inhibitors was also administered.

Approximately one month since the beginning of combination therapy (everolimus 2.5 mg/daily, trough levels 0.7 mcg/L), the patient reported melena, with a hemoglobin drop to 7 g/dl. Upper GI endoscopy showed multiple non-bleeding, angiodysplasias in the gastric fundus and body, that were treated with argon plasma coagulation (APC). ASA was discontinued, and the patient was transfused with packed red blood cells (pRBC), with improvement in hemoglobin values. Everolimus dosage was increased to 4.0 mg/daily over the course of 3 months during which at least two further episodes of acute anemia requiring hospitalization occurred. In the first (everolimus trough levels 4.0 mcg/L), the patient presented with melena and was admitted with a hemoglobin of 4 g/dl, requiring multiple pRBC transfusions. Gastroscopy showed bleeding antral angiodysplasias, that were treated with APC (Fig. 1A). In the second episode -one month later- the patient was admitted with a hemoglobin of 4.6 g/dl (6 units of pRBC transfused, everolimus trough levels 3.6 mcg/L), and gastroscopy showed multiple bleeding erosions with hyperemic and fragile mucosa of the whole stomach, with just a single bleeding spot treated with APC (Fig. 1B).

Literature review suggested a potential role of everolimus as a cause of gastric hemorrhage, the drug was discontinued. Repeat endoscopy identified only two non-bleeding erosions (4 mm), with the remaining endoscopic findings markedly improved (Fig. 1C). At discharge, everolimus was permanently discontinued and immunosuppression with tacrolimus alone optimized (Fig. 2). During follow-up, hemoglobin increased up to 12 g/dl, and the patient experienced no further bleeding episodes.

DISCUSSION

Rare cases of severe hemorrhage have been reported in the literature during treatment with mTOR inhibitors, either everolimus or temsirolimus [6-11]. In five cases previously documented in the literature the patients were undergoing chemotherapy (2 cases for breast cancer, 2 cases for renal cancer, 1 case for metastatic neuroendocrine tumor), and in just one report the patient had previously undergone LT [6-11]. In four of the 5 cases bleeding originated from the upper digestive tract, and in one case

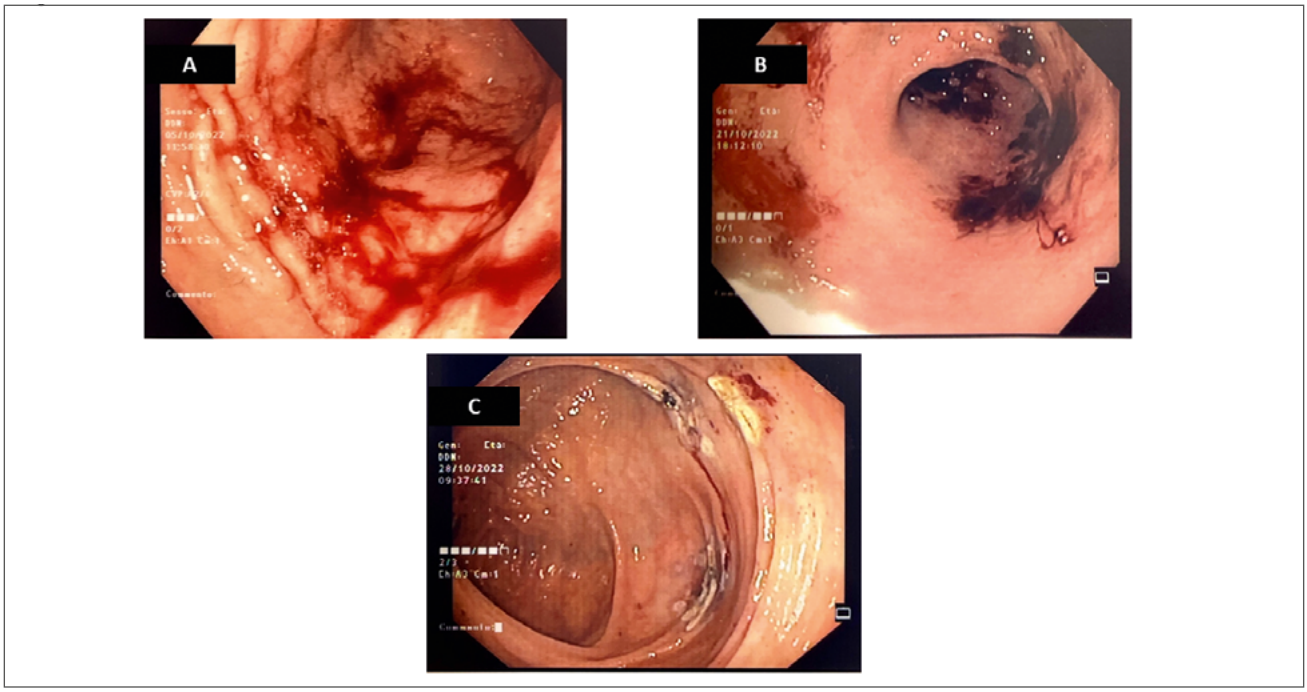

Figure 1. **A**) bleeding antral angiodysplasias that were treated with argon plasma coagulation (everolimus 3.5 mg/daily); **B**) gastric antral bleeding erosions in a context of hyperemic and fragile mucosa (everolimus 4 mg/daily); **C**) endoscopic appearance 1 week after everolimus discontinuation.

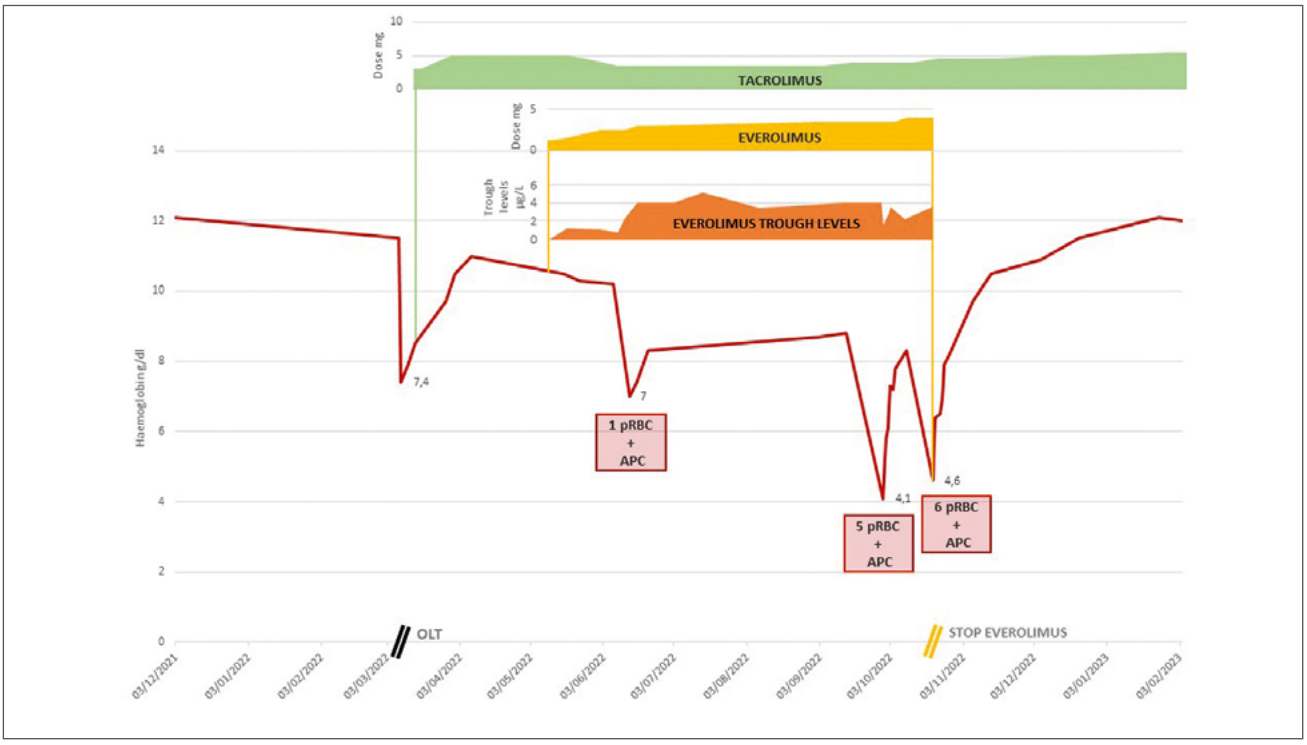

Figure 2. Time course of immunosuppression with drug dosing following liver transplantation, with hemoglobin values and interventions: packed red blood cells (pRBC) transfusions and endoscopic argon plasma coagulation (APC).

it presented as hemorrhagic colitis, while in the only case reported in a LT patient no definite source of bleeding was identified after repeated lower and upper GI tract endoscopic examinations [6-10].

Our patient presented for the first time, even considering his pre-LT clinical history, with GI bleeding that was initially interpreted as multifactorial: he was on prophylactic antiplatelet therapy with ASA and initially had concomitant endoscopic findings of gastric and colic angiodysplasia, all of them endoscopically apparently non-bleeding in the investigations performed after the first episode of melena and anemia. ASA was therefore permanently withdrawn with temporary restoration of acceptable hemoglobin values. However, following increasing dose adjustment of everolimus two additional episodes of life-threatening bleeding occurred, with hemoglobin drop to 4 g/dl in both episodes. During the second hospitalization episode, when an erosive gastropathy was detected, a careful review of the literature raised the suspicion that the causative factor for upper GI hemorrhage might have been pharmacological, as previously reported in a similar case by Gonzales et al., who described an erosive gastritis in a patient treated with everolimus as a second-line treatment for breast cancer [7]. The other reported cases, in fact, even if presenting similar episodes of acute anemia, share endoscopic findings consistent with gastric antral vascular ectasia in the absence of predisposing conditions [6,8-9].

In the only case reported in the literature occurring in a LT patient, both upper and lower GI endoscopies were repeatedly unable to identify a definite source of bleeding, despite the patient required several transfusions and also underwent "blind" transarterial embolization; in this case, co-prescription of apixaban was initially recognized as a potential interaction leading to the bleeding episodes due to the occurrence of bleeding following the introduction of the anti-coagulant, although bleeding persisted even after apixaban withdrawal while the need for transfusions decreased following switch to tacrolimus [10]. In our case, a potential for combined toxicity or a drug-drug interaction was also taken into account, but was ruled out as drugs consistently taken by the patient (ursodeoxycholic acid, allopurinol, tacrolimus) were not associated with this event, and administration of proton pump inhibitors was limited to the period of ASA treatment.

Supporting factors of the causal relationship between everolimus and bleeding episodes were: i) the absence of improvement following ASA withdrawal; ii) the temporal association between optimization of immunosuppression and onset of bleedings; iii) the endoscopic and laboratory improvement observed immediately after everolimus discontinuation; iv) the absence of relapse following everolimus withdrawal. We feel that these clinical findings suffice to support our speculation that everolimus was the causative agent of the repeated upper GI

bleedings observed in our patient. Noteworthy, we found no particular association with everolimus trough levels and the episodes of GI bleeding, and in this regard we feel that this phenomenon may be idiopathic rather than being associated with drug concentrations.

Although the mechanism(s) by which mTOR inhibitors can cause severe digestive hemorrhage remains unclear, we feel that due the increasing use of these drugs in the context of chemotherapy and immunosuppression regimens this case might contribute reporting rare but severe and potentially life-threatening side effects, and help clinicians manage these patients in everyday clinical practice.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

GM, VD, SP: conception and design; GM, VD, SP, EGG: drafting of the article; All authors: critical revision of the article for important intellectual content and final approval of the article; SL, SM, GP, EGG: study supervision; EGG: guarantor of the article.

Ethical consideration

Written informed consent was obtained from patient for data publication.

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