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Colonic ulcers secondary to sirolimus toxicity in a renal transplant recipient

Elena Gonzalez[1], Raquel Fernandez[2], Carlos Jimenez[1], Fernando Renjel[1], Fernando Gil[1], Aurelio Sanz[1], Fernando Escuin[1], Elvira González-Obeso[3], Rafael Selgas[1]

Department of Nephrology[1], Intensive Medicine[2] and Pathology[3].
Hospital Universitario La Paz, Madrid, Spain.

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ABSTRACT

Rapamycin is an immunosuppressive agent which acts as an inhibitor of the mTOR complex. There have been several side effects described. The majority of these drug complications are correlated with sirolimus (SRL) plasma levels.

The appearance of oral aphthous ulcers during treatment with SRL has been extensively described. The ulcers are dose dependant. Oesophageal, gastroduodenal and small bowel ulcers have been described in addition to oral ulcers. Colonic ulcers have not been described to date. We report a case of a patient who underwent renal transplantation and developed colonic ulcers secondary to high rapamycin levels.

Key-Words:
Colonic ulcers; renal transplant; sirolimus toxicity.

INTRODUCTION

Rapamycin is an immunosuppressive agent. Its mode of action lies in interfering with the IL-2-mediated T-cell activation signal by inhibiting the mTOR enzyme complex.

Numerous side effects, including thrombocytopenia, hyperlipidemia, leucopenia, leg oedema, joint pain, pulmonary fibrosis, oral aphthae, delayed wound healing and tendency to wound infections and bleeding have been described. In addition to oral ulcers, oesophageal, gastroduodenal and small bowel ulcers have also been reported.

We report a case of a patient who underwent renal transplantation and developed colonic ulcers secondary to high rapamycin levels, a situation which has not yet been described in the literature.

CASE REPORT

The patient was a 56-year-old male with a history of hypertension, hypertensive cardiomyopathy, type 2 diabetes mellitus and chronic renal failure secondary to diabetic nephropathy who underwent haemodialysis for 17 months. He received a cadaveric renal transplant at age 50 and his primary immunosuppressive therapy was steroids, tacrolimus and mycophenolate mofetil. During the postoperative period he developed acute interstitial graft rejection, which was sensitive to steroid therapy, maintaining a basal creatinine of 1.6 - 2 mg/dl. Four years after the transplant, the patient was diagnosed with well-differentiated trabecular hepatocarcinoma. He underwent surgery and is free of recurrence at present. The hepatic function was apparently not altered by the surgery. There have been neither alterations of the

coagulation nor elevation of the transaminase levels so far. His primary immunosuppressive therapy was changed from tacrolimus to rapamycin. He was maintained on steroids and mycophenolate mofetil was discontinued.

Seven months after this immunosuppressive therapy, he developed a severe episode of 15-stools-per-day of watery diarrhoea, with no pathologic products, with fever, subsequent dehydration and transient renal function worsening, which relatively improved after antibiotic therapy (levofloxacin 500 mg /day during 7 days) and hydration, although two or three stools per day persisted at the time of discharge from hospital. Stool examination, blood and stool cultures were negative, as were Cytomegalovirus antigenemia and the Polymerase Chain Reaction (PCR) technique. A right plantar diabetic ulcer was reported during his stay.

Ten days after discharge from hospital, the patient was re-admitted due to worsening of diarrhoea, consisting of 6 to 8-stools-per-day, fever of 37.7 Celsius degrees and weight loss of 3 kg in the previous three days. Fever was thought to be secondary to the right plantar ulcer, which showed purulent secretion where *Streptococcus sanguinis* and *Fusobacterium necrophorum* were found. After antibiotic treatment the patient improved and the fever disappeared but the diarrhoea remained. Colonoscopy showed multiple ulcers in the entire colonic mucosa, the majority in the descending colon, isolated or grouped, with no exudates or other changes. The findings suggested inflammatory bowel disease (Crohn's disease) to the endoscopist.

Biopsy was taken and histological diagnosis was large bowel mucosa with minimal signs of non-specific acute and chronic inflammation. There was no sign of intranuclear and intracytoplasmic inclusions characteristic of cytomegalovirus (Fig. 1). At this time rapamycin levels were noted to be high (level 36 ng/mL). Drug dosage was reduced and this coincided with an evident improvement of the diarrhoea. Sirolimus levels at discharge were 25.1 ng/mL. Three days after, levels were 15.8 ng/mL. Since then, the patient has been asymptomatic with stable renal function (Fig. 2). Four months after rapamycin levels normalised, a second colonoscopy was carried out in which the disappearance of the ulcers was observed. No reason was found for the elevation of rapamycin levels in this patient.

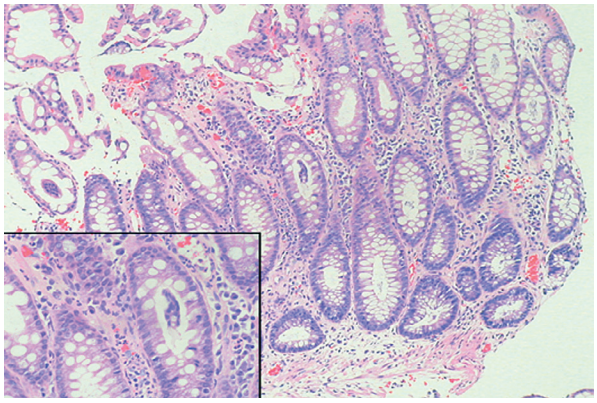

Figure 1

The endoscopic specimen showed minimal acute and chronic infiltrates in the mucosa of the large bowel (HE 100x). The inset shows a zoom (HE 400x) into the mucosa

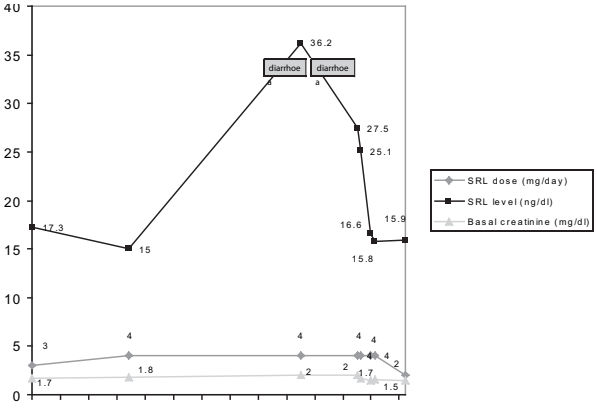

Figure 2

Relation between rapamycin levels and dose given

DISCUSSION

We describe a rapamycin side effect never reported to date. Rapamycin is used as immunosuppressant in solid organs transplantation but it appears to inhibit signalling pathways necessary for cell progression. Thus, it could be used as inhibitor of tumoral neo-vascularisation[1]. It is not free from related complications, however. The most frequent are thrombocytopenia, leucopenia, hypertriglyceridemia, hyper-

cholesterolemia, oral ulcers, leg oedema, joint pain, pulmonary fibrosis, infections and delayed wound healing. The majority of these drug complications are related to sirolimus plasma levels[2,3].

Oral aphthae appearance during SRL treatment has been widely described[4]. These ulcers are more frequent with higher doses of SRL, reaching a frequency of up to 25%[2,4].

The joining of SRL to mTOR inhibits signalling pathways required for cell progression through the G1 phase or entry of the S phase of the cell cycle. Moreover, SRL appears to inhibit smooth muscle cell proliferation, *in vivo* fibrosis and intimal thickening, probably by interfering with local growth factors. Cell repair is similar in all tissues and therefore it is possible that SRL has an effect on this process in the gastrointestinal tract. In addition to oral ulcers, oesophageal, gastroduodenal and small bowel ulcers have also been described, but no large bowel ulcers have been reported[5,6]. This case describes colonic ulcer development coinciding with high rapamycin plasma levels, never reported to date.

This finding must be taken into consideration in the differential diagnosis of renal transplant patients who start with diarrhoea, which is a common complication (depending on the series the frequency was approximately 12.6 %)[7]. Diarrhoea is usually due to infection (Cytomegalovirus and *Clostridium difficile*) and secondary to immunosuppressant agents, such as mycophenolate mofetil. While SRL has lower incidence of diarrhoea[8] as compared to other immunosuppressive drugs, its frequency increases in parallel with its plasma levels.

Other less frequent causes of diarrhoea are lymphoproliferative diseases, colonic cancer, graft-*versus*-host disease and inflammatory bowel disease. In our case, the last one was ruled out after anatomopathologic study[7,8]. It is appropriate to underline inflammatory bowel disease which although uncommon, is difficult to distinguish by endoscopy from ulcers secondary to rapamycin, which will have implications on treatment.

In conclusion, colonic ulcers, possibly coupled with elevated blood levels, can be a reversible secondary effect of sirolimus.

Conflict of interest statement. None declared.

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Correspondence to:
Dr Elena González García
Hospital La Paz (8ª Planta, Hospital General)
Pº Castellana, 261
28046 Madrid, Spain
E-mail: egonzalez_sp@hotmail.com