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Successful management of anemia with sirolimus in blue rubber bleb nevus syndrome: case report and update

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ABSTRACT

Blue rubber bleb nevus syndrome (BRBNS) is a rare disorder with characteristic skin hemangiomas and vascular malformations, mostly in the gastrointestinal (GI) tract.

The GI lesions are mainly located in the stomach and small intestine, usually more than a hundred, leading to gastrointestinal bleeding and severe chronic anemia. Parenteral iron infusions and scheduled transfusions are frequently necessary.

We describe the case of a 21-year-old male with anemia secondary to BRBNS, who becomes unresponsive to octreotide and shows an excellent response to sirolimus (SRL), dismissing the intravenous iron supplementations and being free of transfusions. During the treatment, the patient presents avascular hip necrosis, which is adequately treated with an injection of stem cells with complete recovery, and without the suspension of SRL. Two years later, adequate response persists with no other relevant side effects.

Key words: Anemia. Cutaneous hemangioma. Gastrointestinal tract. Vascular malformation. Sirolimus. Rapamycin. Blue rubber bleb nevus syndrome.

INTRODUCTION

The blue rubber bleb nevus syndrome (BRBNS) is a rare disorder consisting in multiple vascular malformations mainly along de gastrointestinal tract and skin. The more frequent and serious presentation is GI bleeding, that can require lifelong iron replacement, and in severe cases, repeated transfusions.

The etiology is unknown, and although the majority of cases are sporadic, it has been also described an autosomal dominant transmission in some cases, with the responsible locus in 9p chromosome (1,2).

The lesions consist of deep dark blue-black and gummy consistency. No malignant transformation has been reported and the morbidity and mortality depend mostly on chronic intestinal bleeding, intussusception and bowel infarction.

Sirolimus (SRL) is a potent immunosuppressant agent used to avoid transplant rejection. It has antiangiogenic and antineoplastic properties, and successful treatment with SRL has been reported in several vascular and lymphatic conditions. The first use of SRL in the management of BRBNS was in 2012, and since then some other cases have been reported (3). In this case report, the first successful case published in Spain of BRBNS treated with SRL is described.

CASE REPORT

We present the case of a 21-year-old boy, diagnosed of BRBNS at the age of five, with a history of multiple vascular lesions in the skin, liver and GI tract. He underwent a bowel resection in childhood due to an intussusception caused by intestinal lesions.

Anemia was controlled with parenteral iron supplementations but in 2011 gastrointestinal blood losses worsened and repeated transfusions were needed. More than 100 lesions along the small intestine were described in the evaluation with capsule endoscopy. Octreotide was started then at a dose of 20 g monthly, associated to ferric carboxymaltose (1,000 mg monthly), showing good response in hematologic parameters, maintaining hemoglobin levels between 9-11 g/dl.

In August 2014, the treatment was temporarily stopped because of an avascular osteonecrosis in the left hip, and weekly transfusions were again necessary until octreotide treatment was restarted again.

Concomitantly, from 2012 to 2016, different endoscopic approaches were carried out in accessible lesions: endoscopic sclerosis with polidocanol, argon plasma photocoagulation and endoscopic ligature with endoloop (Olympus PolyLoop Ligation Device), but no objective improvement was noticed.

In 2017, after five years of octreotide treatment, blood transfusions were again necessary, and rapamicyn (SRL) was proposed as a compassionate-use. He underwent a traumatologist examination and a close monitoring was programmed because of the background of the hip avascular osteonecrosis. Few weeks after starting sirolimus, at a dose of 0.07 mg/kg/day (5 mg/day), hemoglobin levels increased from 8.5 to 12 g/dl, and we decided to decrease the dose to 3.5 g/day, with analytical stability.

Six months later, the patient presented with contralateral hip discomfort and a magnetic resonance image (MRI) confirmed avascular femoral osteonecrosis. A surgical approach with stem cells injection allowed an adequate clinical evolution.

Almost two years after starting SRL, the patient maintains an excellent control of anemia and gastrointestinal bleeding, and no other side effect of interest have appeared so far.

DISCUSSION

Currently, there exists no curative therapy for BRBNS and no consensus regarding the management of these patients. Palliative treatments include iron supplements and blood transfusions. Pharmacological therapy with octreotide, corticosteroids and hormonal therapy have been described, but none of them has demonstrated an adequate control of anemia. Endoscopic approach to remove accessible lesions or surgical resections are proposed, but the high number of malformations along the small bowel prevents an entire management.

Yüksekkaya et al. report the use of SRL in the treatment of BRBNS for first time, as a safe and efficient agent at the dose of 0.05-1 mg/kg (3).

The exact mechanism of action of SRL is not well known. The antineoplasm activity is based on the normalization of mammalian target of rapamycin (mTOR) signaling pathway, and the antiangiogenic action seems to be linked to the inhibition of the vascular endothelial growth factor (VEGF) receptor (2-4,6). c-Kit receptor has been expressed in small vessels in patients with BRBNS, suggesting its association with the development of these venous malformations (2-4,6). The pharmacological c-kit-inhibition could offer new ways of treatments.

Since Yüksekkaya's report, more cases have been described using SRL for BRBNS. Table 1 summarizes them. Most of the cases use doses between 0.05 and 0.1 mg/kg, although in pediatric patients it is calculated as a function of the body surface (0.5-2 mg/m^2) (2-4,6). About half of the cases determine SRL blood concentration, especially in pediatrics, with a more common target valley concentration between 5 and 10 ng/ml, but there is no clear evidence about its necessity (1).

In the present case, we report a possible secondary effect associated to the use of rapamicin. The most frequent adverse reactions are hyperlipidemia (51%), thrombocytopenia (10-18%) and leukopenia-topenia (10-18%) (2,5). Other adverse effects are a higher risk of infections, arthralgias, mucositis and alterations in liver and/or renal function (4). Nonetheless, along the reported cases, it appears to be a well-tolerated treatment with no significant side effects and a small percentage of discontinuation.

Regarding avascular necrosis (AVN) and SRL, very few cases have recorded this possible association, and it has not been identified as an independent risk factor for avascular hip necrosis neither for osteonecrosis of the jaw after kidney transplantation. In our case, a relationship can be presumed between the avascular hip necrosis and the use of SRL, however, the patient had suffered a similar side effect in the contralateral hip under octreotide, which may be linked to a greater personal susceptibility.

In conclusion, SRL is a useful treatment in the management of patients with BRBNS, significantly improving the patient's quality of life and avoiding potential risks of blood transfusions and aggressive surgical approaches. However, some important questions must be answered, as there are no clear guidelines regarding dosing regimen, and the

long-term safety, as usually the discontinuation of the treatment is followed by the recurrence of the gastrointestinal bleeding. We recommend a high index of suspicion of avascular necrosis if hip pain appears, to provide an early management of this pathology that prevents complications.

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Table 1. Cases reported for the use of sirolimus for BRBNS, including dose and secondary effects

Author (year)	*Number of patients*	*Age (years): mean (range)*	*Daily sirolimus dose*	*Sirolimus level (ng/ml)*	*Persistence with treatment (months)*	*Response to sirolimus*	*Secondary effects*
Yukksekkaya H et al., 2012 (3)	1	8	0.05-0.1 mg/kg	1-5	20	↓size of lesions ↓ number of lesions ↓ episodes of gastrointestinal bleeding ↑ Hb Stop transfusion	↑cholesterol
Taddio A et al., 2013 (7)	1	3	NA	NA	5	↑ Hb ↓ size of lesions	-
Warner B et al., 2015 (2)	1	18	4 mg	NA	9	↑Hb	-
Özgönenel B et al., 2015 (5)	1	18	1.6 mg/m^2 → 1.2 mg/m^2 → 0.6 mg/m^2	6.6-7.3 → 3.4-5.5 → 2-3.1	12	↑Hb ↓ episodes of gastrointestinal bleeding and hospitalizations	thrombocytopenia leukopenia
Ferrés-Ramis L et al., 2015	1	8	0.05 mg/kg → 0.025 mg/kg	NA	12m	↑Hb ↓size of lesions Stop transfusion	
Salloum R et al., 2016 (4)	4	6.5 (2-16)	1.6 mg/m^2	10-13	21m (18-26 m)	↑ Hb ↓ size of lesions	0/3 mucositis 1/0 neutropenia

Ünlüsoy Aksu et al., 2017 (1)	1	11	2.5 mg → 1 mg → 0.5 mg	10-15	20 m	↑ Hb ↓ size of lesions	Oral ulcers
Akyuz C et al., 2017 (8)	1	6	1.6 mg/m^2 → 2 mg/m^2	5-12	17 m	↑ Hb ↓ episodes of gastrointestinal bleeding ↓ size of lesions	-
Juliana R Gildener-Leapman et al., 2016 (9)	1	1.5	0.6 mg	NA	6m	X HD ↓ tamaño	-
Kizilocak H et al., 2018 (6)	4	6.5 (4-15)	1.2 mg/m^2	NA	72 (36-108)	↑ Hb ↓ size of lesions Stop or ↓ transfusion	1/0 severe soft tissue infection: stop
Ogu U et al., 2018 (10)	1	19	0.05 mg/kg	5-10	60	↑ Hb Stop transfusion ↓ episodes of gastrointestinal bleeding	
Cardoso H et al., 2016	1	19	2 mg	NA	12	↑ Hb ↓ size of lesions Stop transfusion	
Wang KL et al., 2018	1	12	0.7 mg	6.2-11.9	12	↓ size of lesions ↑ Hb Stop transfusion	
Fernandez et al.	1	21	3.5 mg	NA	18	↑ Hb Stop transfusion	Hip avascular necrosis

Adapted from Wang KL, Ma SF, Pang LY, et al. Sirolimus alternative to blood transfusion as a lifesaver in blue rubber bleb nevus syndrome: a case report. Medicine (Baltimore) 2018;97:e9453.

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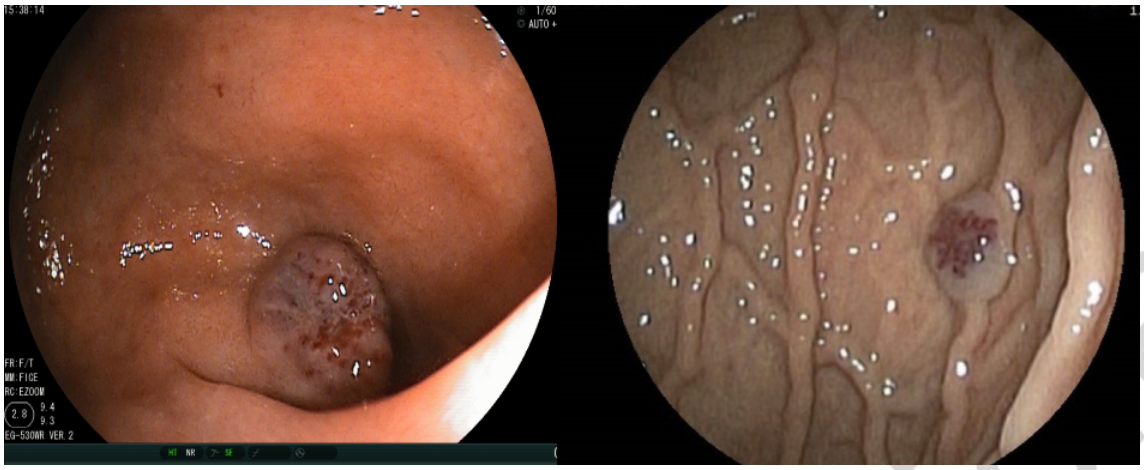

Fig. 1. Gastric (A) and duodenal (B) lesions found in upper gastrointestinal endoscopy.

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Fig. 2. Hemoglobin concentrations and units of blood transfusions before and after sirolimus: 2011-2019.