DOI: 10.1111/pde.14506

Pediatric Dermatology WILEY

Long-term sirolimus treatment in blue rubber bleb nevus syndrome: Case report and review of the literature

Doris Weiss MD[1,2] | Anne Teichler MD[1] | Peter H. Hoeger MD[1,3]

[1]Department of Paediatric Dermatology, Catholic Children's Hospital Wilhelmstift, Hamburg, Germany

[2]Department of Dermatology, Medical University of Vienna, Wien, Austria

[3]Department of Paediatrics, Catholic Children's Hospital Wilhelmstift, Hamburg, Germany

Correspondence
Peter H. Hoeger, MD, Catholic Children's Hospital Wilhelmstift, Liliencronstr. 130, D22143 Hamburg, Germany.
Email: hoeger@kkh-wilhelmstift.de

Abstract

Blue rubber bleb nevus syndrome is a rare vascular syndrome characterized by continuous eruption of vascular nodules in the skin, mucous membranes, and solid organs due to somatic activating mutations of the angiopoietin receptor *TEK* gene. It may be complicated by acute life-threatening hemorrhage and localized intravascular coagulation. We report an 11-year-old girl with complicated blue rubber bleb nevus syndrome treated with sirolimus since the age of 2. We review the literature on sirolimus therapy for children with blue rubber bleb nevus syndrome.

KEYWORDS

blue rubber bleb nevus syndrome, hemorrhage, localized intravascular coagulation, long-term therapy, sirolimus

1 | BACKGROUND

Blue rubber bleb nevus syndrome (BRBNS, Bean syndrome) is a rare vascular malformation syndrome caused by a somatic activating mutation of the angiopoietin receptor *TEK (TIE2)* gene.[1,2] It is characterized by recurrent eruptions of multiple vascular nodules within the dermis, intestinal mucous membranes and parenchymatous organs which come and go. Erosion of intestinal lesions leads to acute or chronic hemorrhage, sometimes life-threatening. Bleeding tendency is further compounded by chronic localized intravascular coagulation (LIC).[3,4] Due to the extent of mucosal involvement, surgical treatment is often not feasible. BRBNS thus frequently had a lethal outcome until the advent of sirolimus treatment first described for this indication in 2012.[5] Here, we report the long-term outcome of a child with BRBNS treated with sirolimus for 9 years, and briefly review the literature.

2 | CASE REPORT

A newborn girl presented to our pediatric department dermatology shortly after delivery, following an uneventful pregnancy. Clinical examination revealed generalized blueish, papulonodular lesions of a rubbery consistency each measuring 2-4 mm in diameter (Figure 1A). A subcutaneous tumor on the posterior aspect of the neck, previously undetected by prenatal ultrasound, was noted (Figure 1B). Ultrasound and MRI of the neck region revealed a slow-flow vascular tumor extending from the neck musculature toward the intraspinal and epidural space, causing compression of the cervical spinal cord. Initial differential diagnoses included cutaneous extramedullary hematopoiesis ("blueberry muffin baby"), multifocal infantile hemangioma, multifocal lymphangioendotheliomatosis with thrombocytopenia and BRBNS. A skin biopsy of the left thigh revealed a vascular tumor in the reticular dermis and adjacent subcutaneous fat layer without any signs of malignancy (Figure 1C). Two somatic mutations of *TEK*, each at a variant allele frequency of 2% (c.2960A>G, p. [Tyr897Cys] and c.2753G>T, p. [Arg918Leu]), were later identified in a tissue sample but not in the blood, confirming the diagnosis of BRBNS (Institute of Human Genetics, University of Freiburg, Germany).

Oral treatment with propranolol (2 mg/kg/d for 3 months) was started on the initial assumption of multifocal infantile hemangiomatosis but did not prevent further growth of the nuchal lesion, which led to progressive compression of the cervical spinal cord with concern for impending paralysis. Dexamethasone (0.2 mg/kg) was administered preoperatively, and the patient underwent urgent neurosurgical decompression and resection of the vascular tumor. At 10 months of age, the patient developed hemarthrosis of her right

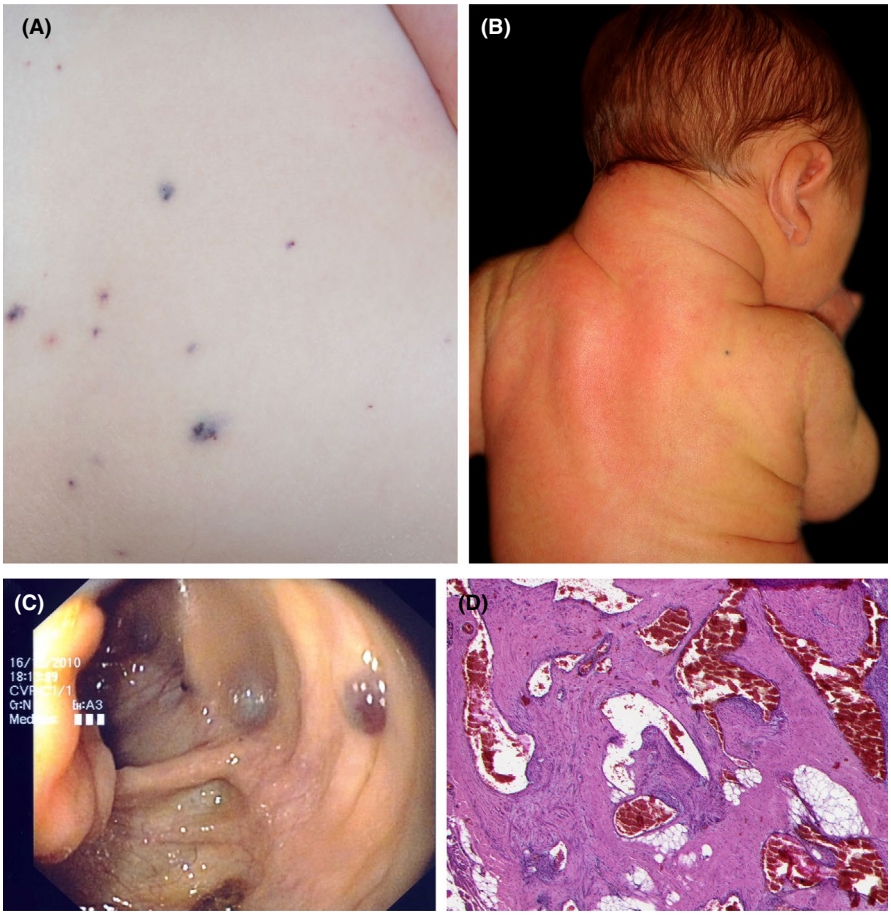

FIGURE 1 A, Disseminated bluish papules and nodules scattered over the trunk. B, Large congenital subcutaneous tumor on the posterior neck. C, Vascular nodules (venous malformations) throughout her gastrointestinal mucosa. D, Histopathology reveals characteristic BRBNS with malformed venous vessels with thick myoid vessel walls (H&E 40×, Courtesy Dr Heinz Kutzner)

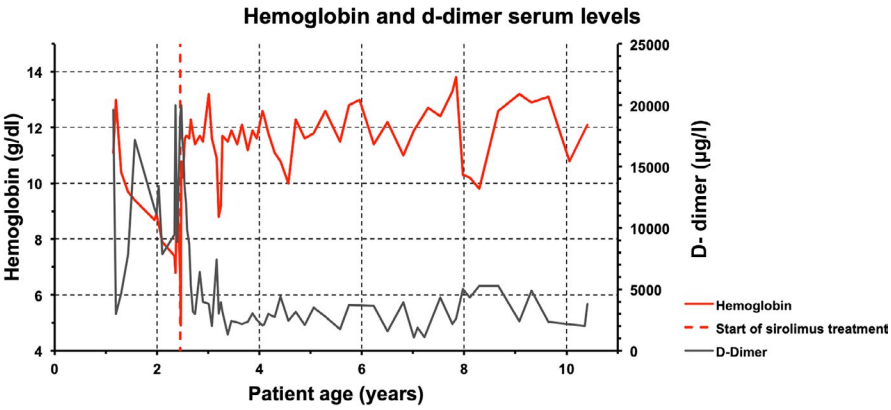

FIGURE 2 Laboratory values before and after the initiation of sirolimus therapy. Hemoglobin stabilized at near-normal levels without further need for blood transfusions. Reference value: 11.0-14.0 g/dL. D-dimer levels as a marker of subclinical disseminated intravascular coagulation decreased with therapy. Reference value: 0-500 µg/L

knee and spontaneous recurrence of the preexisting nuchal subcutaneous malformation. Significantly elevated D-dimer levels were indicative of ongoing fibrinolysis (Figure 2). She suffered recurrent episodes of uncontrollable gastrointestinal hemorrhage, requiring multiple blood transfusions. Total body MRI scan and upper and lower GI tract endoscopy (Figure 1D) revealed numerous unresectable venous malformations, extending from the gastric to the intestinal and colonic mucosa.

At the age of 2 years, treatment with sirolimus was initiated and slowly increased to a dose of 0.1-0.2 mg/kg/d in order to maintain serum trough levels of 8-10 ng/mL.[6] After initiation of therapy, the patient's hemoglobin levels rapidly stabilized without further requirements of blood transfusions, and d-dimer levels as a marker of localized intravascular coagulation dropped significantly (Figure 2). The patient developed hyperlipidemia (cholesterol 232 mg/dL, normal < 200 mg/dL; triglycerides 243 mg/dL, normal < 200 mg/dL) and was started on atorvastatin at the age of 5 years. Otherwise sirolimus therapy was well-tolerated and led to stabilization of hemoglobin and decrease of d-dimer levels (Figure 2). Regular checks of renal, liver, and hematological parameters were within normal ranges.

Subsequent resections of an intra-articular venous malformation at the age of 7 years and of a subcutaneous lesion at the age of 8 years were tolerated well. It is noteworthy that temporary interruptions of sirolimus treatment due to surgery led to recurrent

TABLE 1 Summary of published reports on sirolimus therapy in pediatric patients with BRBNS

No.	Age at start of sirolimus (y)	Sex	Prior complications	Previous Tx	Daily dose of sirolimus	Duration of sirolimus therapy	Side effects	Ref.
1	8	F	GI bleeding, large cutaneous lesion in scapular area	Multiple BT, surgery, prednisolone, interferon-α, propranolol, aminocaproic acid	0.05-0.1 mg/kg	23 mo	Hypercholesterolemia	8
2	15	F	GI bleeding, severe iron deficiency anemia	Intestinal surgery, tracheostomy, sclerotherapy, aminocaproic acid	0.05 mg/kg	60 mo	None	9
3	0, 1, 2, 5, 12	3 M 2 F	GI bleeding, muscular and subcutaneous VMs, CNS involvement	Surgical resection, sclerotherapy, thalidomide, tranexamic acid	1.6 mg/m^2/d	10 mo to 7 y	None reported	5
4	3	M	GI bleeding, severe iron deficiency anemia, large subcutaneous swelling ankle region	Propranolol, surgery	N/A	6 mo	None reported	11
5	18	F	GI bleeding, lesion in thoracic spine	Surgery, multiple BT	1.6 mg/m^2/d reduced to 0.6 mg/m^2/d	12 mo	None reported	12
6	8	UNK	GI bleeding, large congenital tumor in fronto-orbital region	Multiple BT, surgery, laser ablation of intestinal VMs	0.05 mg/kg, reduced to 0.025 mg/kg	12 mo	None reported	13
7	18	M	Supraglottic VM requiring tracheostomy	Multiple BT, thalidomide, multiple bowel resections, argon plasma coagulation	4 mg/d not otherwise specified	9 mo	None reported	14
8	2, 3, 10 16	3 F 1 M	GI bleeding, cutaneous, visceral and muscular lesions	Multiple BT, LMW heparin, sclerotherapy, surgical resection	1.6 mg/m^2/d	48 mo	Mucositis, neutropenia	15
9	18	M	GI bleeding, muscular and subcutaneous VMs	Multiple BT, multiple bowel resections, thermal argon ablation	2 g/d not otherwise specified	12 mo	None reported	16
10	6	F	GI bleeding, consumptive coagulopathy	Multiple BT, steroids, sclerotherapy, interferon	1.6-2 mg/m^2/d	17 mo	None reported	17
11	3	M	GI bleeding, VM involving achille's tendon preventing normal walking	N/A	1.2 mg/m^2/d	6 mo	None reported	18
12	4, 6, 7, 15	2 M 2 F	GI bleeding, muscular, pulmonary VMs	Steroids, thalidomide, bevacizumab, interferon-α, cyclophosphamide, tranexamic acid, propranolol	1.2 mg/m^2/d	2-54 mo	Severe soft tissue infection	19
13	10	M	GI bleeding	Propranolol, omeprazole	0.1 mg/kg	20 mo	Oral ulcers	20
14	12	F	GI bleeding	Multiple BT, surgical resection	0.04 mg/kg	12 mo	None reported	21
15	18	M	GI bleeding, subcutaneous VMs	Multiple BT, surgical resection, endoscopic cauterization	0.02 mg/kg (reduced to alternate-day regimen after 2 mo)	12 mo	None reported	22

Abbreviations: BT, blood transfusion; GI, gastrointestinal; VM, venous malformation.

intestinal bleeding, as evidenced by positive fecal blood tests. At 11 years of age, the patient remains in a good state of general health and has been receiving regular physical therapy for restricted mobility in her right knee. Currently, she visits our department at 3-month intervals and is regularly monitored for laboratory parameters (sirolimus trough levels, hemoglobin and platelet count, blood lipids, d-dimer, fibrinogen) and fecal blood.

3 | DISCUSSION

Sirolimus is a protein-kinase inhibitor of mammalian target of rapamycin (mTOR) that is widely utilized as an immunosuppressive and antineoplastic drug. Due to its anti-angiogenetic properties, it has also proved to be an effective treatment option for various vascular tumors. Since the first report of its efficacy in an 8-year-old patient with BRBNS in 2012, this finding has been corroborated by several other reports.[5,7–21] Nevertheless data on long-term sirolimus treatment in children with BRBNS are scarce and a standard approach concerning dosage, monitoring of target trough levels and overall duration of therapy has yet to be established.

Our report on 9 years of sirolimus treatment in a patient with BRBNS is the longest treatment duration reported to date. A total of 25 pediatric patients with BRBNS treated with sirolimus have been described previously (Table 1). Age at start of therapy, dose, and reported duration of therapy vary widely. Sirolimus was initiated at a mean age of 10 years (range: 2-18 years). An average sirolimus dose of 0.05 mg/kg/d (range: 0.02-0.1 mg/kg/d) or 1.42 mg/m^2 (range: 0.6-2 mg/m^2) was used with mean sirolimus trough levels of 7.5 ng/mL (range: 1-15 ng/mL). Reported duration of therapy ranged from 2 months to 7 years (mean: 22.3 months).

While symptoms usually improve with treatment, similar to our patient, a swift recurrence is observed with temporary discontinuation of therapy.[5,9] Different target trough levels have been recommended in the literature. Originally, trough levels as high as 10-15 ng/mL were suggested,[7] but successful management of BRBNS has been described anecdotally at lower trough levels ranging from 1 to 5 ng/mL.[7,8,12,22] However, it appears that chronic intestinal bleeding persisted in some of these cases, albeit at low levels.

In the absence of prospective and controlled clinical studies, it is obviously difficult to make firm sirolimus dosing recommendations. Even though lower drug levels might generally be associated with fewer side effects, it is debatable whether sirolimus truly exhibits its full efficacy when administered at lower doses.[22–24] We observed that a decrease in sirolimus trough levels below 7 ng/mL was generally accompanied by a rise in d-dimer levels (*data not shown*).

Localized intravascular coagulation with elevated d-dimer levels occurs in 30% of all pediatric VM and is more common in large or multifocal VM.[25] D-dimer levels were previously shown to be a useful marker of efficacy as they decrease with sirolimus therapy; hence, it was suggested that long-term sirolimus therapy improves LIC in slow-flow VM.[26] Our case suggests that at maintenance trough levels of 8-10 ng/mL, bleeding tendency and coagulopathy can be controlled with minimal adverse effects.

This case supports previous findings that trough levels below the originally recommended 10-15 ng/mL are sufficient to obtain long-term disease control in BRBNS without serious side effects.[6,7] However, sirolimus does not prevent the formation of new vascular lesions, and in view of the rapid deterioration following each short-term interruption of therapy, we anticipate that our patient will require life-long sirolimus treatment in order to avoid life-threatening complications. Early initiation of therapy is ideal to prevent bleeding complications, as in our case; but the optimal timing, dosage, and duration of therapy remain to be established by randomized controlled trials. This case highlights the long-term safety and efficacy of sirolimus treatment in a child with BRBNS.

ORCID

Peter H. Hoeger https://orcid.org/0000-0003-3268-7479

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How to cite this article: Weiss D, Teichler A, Hoeger PH. Long-term sirolimus treatment in blue rubber bleb nevus syndrome: Case report and review of the literature. *Pediatr Dermatol*. 2021;38:464–468. https://doi.org/10.1111/pde.14506