Case Report

Successful Management of Blue Rubber Bleb Nevus Syndrome (BRBNS) with Sirolimus

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1. Introduction

Vascular anomalies can be divided into two broad categories, according to the International Society for the Study of Vascular Anomalies (ISSVA) system: vascular malformations and vascular neoplasms [1]. Vascular malformations include slow-flow malformations (with venous, capillary and/or lymphatic components) and fast-flow malformations (with arterial components); while vascular neoplasms undergo mitosis and include such lesions as infantile hemangioma, congenital hemangioma, kaposiform hemangioendothelioma, tufted angioma, hemangiopericytoma, and angiosarcoma [2]. Blue rubber bleb nevus syndrome (BRBNS) is primarily considered a slow-flow venous malformation, although there has been a single case report which includes a lymphatic component [3]. BRBNS usually presents in infancy and childhood and rarely in adulthood [3]. Lesions are blue, rubbery, and compressible, and they occur in several organ/systems and most commonly occur within the skin and gastrointestinal (GI) tract [4].

2. Case Description

A Hispanic female initially presented at three years of age with a history of oropharyngeal bleeding since birth and diffuse skin vascular malformations. Upper and lower GI endoscopies revealed multiple vascular anomalies throughout the entire tract. She was subsequently diagnosed with blue rubber bleb nevus syndrome based on clinical and endoscopic findings. Due to GI bleeding, chronic iron deficiency anemia, and the increased need for blood transfusions, she underwent surgical removal of multiple blebs from her stomach, small intestine, and colon. In addition, she underwent a right colectomy, gastrostomy for tube feedings, and a tracheostomy due to multiple tracheal lesions. At the age of 6.5 years, she was referred to pediatric hematology for the management of anemia. She had long-standing iron deficiency anemia due to significant blood loss from GI bleeding, despite previous RBC transfusions, and intravenous iron therapy. To help control bleeding, she underwent frequent sclerosing therapies to multiple lesions, including the
pericervical lesions. An oral aminocaproic acid (Amicar) trial of 10 days duration was not successful to reduce GI bleeding. Despite the above interventions, she remained severely anemic (hemoglobin levels 5.2 gm/dL to 7 gm/dL) and required frequent blood transfusions, as often as every 1–4 months. Due to the significant GI bleeding, her stools were black, tarry, often with bright red blood, occurring 3–4 times a week. At age 15, a trial of daily sirolimus therapy was initiated, based on a case report by Yussekkaya et al. [4], at a dose of 0.05 mg/kg/dose and levels followed with a target range of 5–10 ng/ml. Within 2 months of initiating sirolimus therapy, she experienced cessation of hematochezia and melena, and her hemoglobin has since remained above 11 g/dl (Figure 1). She is now over 60 months into therapy, remains without anemia, and has not required further blood transfusions. She remains mildly iron deficient to date, most likely due to decreased ability to adequately absorb oral iron due to the blebs and prior GI surgery. No adverse drug reactions have occurred.

3. Discussion

Blue rubber bleb nevus syndrome is a rare congenital disorder with hallmarks of venous malformations on the skin and visera. The skin and soft tissue lesions rarely cause debilitating disease and are mostly a cosmetic concern [4]. In contrast, the GI lesions are a major cause of morbidity. Patients usually develop severe chronic iron deficiency anemia, requiring multiple transfusions due to persistent GI losses [4].

To date, there is no curative treatment for BRBNS. Management options that have been attempted include iron therapy, blood transfusions, surgical interventions, and pharmacologic agents [4]. Iron therapy and blood transfusions have been employed to alleviate anemia from GI losses. Surgery has been used to eradicate blebs from the skin, soft tissue, or GI tract; however, the blebs eventually recur. Other modalities including laser photocoagulation and sclerotherapy have been applied with limited success. Pharmaceutical agents such as propranolol, octreotide, corticosteroids, interferon alpha, thalidomide, antifibrinolytics, and most recently sirolimus have also been utilized. These have been used based on extrapolation of their efficacy in infantile hemangiomas and other vascular anomalies.

Sirolimus is an immunosuppressant drug that has both antiangiogenic and antineoplastic properties. Its mechanism of action is via pathway inhibition of the mammalian target of rapamycin (mTOR), a serine/threonine kinase regulated by phosphoinositide-3-kinase (PI3K) [5]. It has been used successfully in the management of several vascular anomalies such as kaposiform hemangioendothelioma, tufted angioma, and lymphatic malformations [1]. The first case report describing response of BRBNS to sirolimus was published in 2012 by Yussekkaya et al. [4]. Following that there have been several other reports also describing response to sirolimus [3, 6–14]. Table 1 details the various reports in the literature so far that have described the use of sirolimus for BRBNS.

The exact mechanism of action of sirolimus in BRBNS remains unclear, but proposed mechanisms of action include inhibition of ligand-binding-induced signaling through VEGFR-3 (vascular endothelial growth factor receptor-3) on lymphatic endothelial surface, which would normally result in activation of the PI3K/Akt/mTOR pathway [3, 5]. In addition, c-kit (stem cell growth factor receptor) expression from small venous vessels has been described [15] and has been proposed as a possible mechanism of action, given that c-kit is a tyrosine kinase upstream of mTOR [3].

There exists a dilemma as to what constitutes appropriate duration of therapy. Our patient continues on sirolimus at a dose of 1.2 mg/day (0.024 mg/kg/dose), with target trough level of 2–4 ng/mL and has not experienced any side effects. Her hemoglobin and symptoms remained controlled. Of note, when sirolimus was held for a surgical procedure due to concerns for postsurgical wound healing, her GI bleeding returned within 3 days of discontinuation. Further studies are needed to determine if sirolimus can be safely discontinued, without disease relapse.

In conclusion, sirolimus may be used in management of patients with BRBNS. Our case report describes resolution of GI bleeding and obviation of the need for multiple blood transfusions following initiation of sirolimus therapy. We propose this as an alternative therapy for the treatment of symptomatic BRBNS, especially when other conventional therapies have proved to be unsuccessful.
| Article authors | Article title | Article journal | Article year | Patient | Response to Sirolimus | Sirolimus dose | Sirolimus level | Time to improvement |
|----------------|--------------|----------------|-------------|---------|----------------------|----------------|-----------------|--------------------|
| Yuksekkaya H, Ozbek O, keser M, Toy H [4] | Blue rubber bleb nevus syndrome: successful treatment with Sirolimus | Pediatrics | 2012 | 8 yo F; GI bleeding, not responsive to prednisolone, propranolol, aminocaproic acid, and alpha-interferon therapy | Hemoglobin improved from 7 gm/dL to 14gm/dL (with iron supplement); | 0.05–0.1 mg/kg | 1–5 ng/mL | 2 months. Symptoms returned if sirolimus discontinued |
| Taddio A, Benelli E, Pierobon C, Martelossi S, Berti I, Ventura A [6] | From skin to gut | J Pediatr | 2013 | 3 yo M; severe iron deficiency anemia, large subcutaneous swelling on right ankle, and multiple skin lesions | Hemoglobin improved from 6.4gm/dL to 'stable' | not available (NA) | NA | 6 months |
| Ozgonenel B, Martin A [9] | Low-dose sirolimus controls recurrent iron deficiency in a patient with blue rubber bleb nevus syndrome | Pediatr Blood Cancer | 2015 | 18 yo F; GI bleeding and iron deficiency anemia | Hemoglobin improved from 5 gm/dL to ~14 gm/dL; | 1.6 mg/m²/day divided BID; reduced to 0.6 mg/m²/day | 10–15 ng/mL, then goal levels reduced <2.0–3.1 ng/mL | “after starting sirolimus” |
| Ferrés-Ramis L, knöpfel N, Salinas-Sanz J, Martin-Santiago A [8] | Rapamycin in the treatment of blue rubber bleb nevus syndrome: Sirolimus is a successful treatment for recurrent iron deficiency anemia in blue rubber bleb nevus syndrome | Actas Dermo-Sifiliográficas (English Edition) | 2015 | 8 yo with congenital cutaneous and GI vascular malformations | Decreased size of lesions, normalized hemoglobin | Initial dose 0.05mg/kg, reduced to 0.02mg/kg | | Within a month |
| Warner B, Butt A, cairns S [7] | J Pediatr Gastroenterol Nutr | 2015 | 18 yo M; hemangioma, tracheostomy, anemic; thalidomide—discontinued due to side effects; multiple bowel resections to remove vascular malformations | Hemoglobin 6.9 gm/dL, anemia resolved | 4 mg daily | | |
| Salloum R, Fox CE, Alvarez-Allende CR, et al. [3] | Response of blue rubber bleb nevus syndrome to sirolimus treatment. | Pediatr Blood Cancer | 2016 | 2–16 yo, cutaneous, GI tract, visceral and muscular lesions | Decreased size of lesions, decreased pain, normalized hemoglobin | 0.8 mg/m² every 12 hour dose titrated to target trough level between 10 and 13 ng/mL | | less than 3 months |
| Article authors                  | Article title                                                                 | Article journal            | Article year | Patient Description                                                                                                                                                                                                 | Response to Sirolimus                                                                 | Sirolimus dose | Sirolimus level | Time to improvement |
|---------------------------------|-------------------------------------------------------------------------------|----------------------------|--------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|----------------|------------------|---------------------|
| Cardoso H, Dias JA, Silva M, et al. [10] | Gastrointestinal: successful treatment with sirolimus of a patient with blue rubber bleb nevus syndrome | *J Gastroenterol Hepatol*  | 2016         | 19 yo M; multiple visceral, muscular, and subcutaneous vascular lesions, complicated with chronic local pain and GI bleeding requiring RBC transfusion (total of 74); treatment with thermal argon ablation and sclerosis and segmental jejunoileal surgical resections, propranolol and ferric carboxymaltose | Improved blood loss, asthenia, and decreased size of lesions; hemoglobin improved by 6 gm/dL | 2 gm/day       | 2.0–3.8 ng/mL    | About 5 months      |
| Ünlüsoy Aksu A, Sari S, Eğritaş Gürkan O, Dalgic B [11] | Favorable response to sirolimus in a child with blue rubber bleb nevus syndrome in the gastrointestinal tract | *J Pediatr Hematol Oncol*  | 2017         | 11 yo M with vascular malformation in GI tract | Normalized hemoglobin in 2.5 months, decreased lesions in 5 months | 0.1 mg/kg/d   | 1–5 ng/mL        | 2.5–5 months        |
| Akyuz C, Susam-Sen H, Aydin B [12] | Blue rubber bleb nevus syndrome: promising response to sirolimus              | *INDIAN Pediatr*            | 2017         | 6 yo F with skin lesions, GI tract and consumptive coagulopathy (platelets 77K, fibrinogen 104 mg/dL, d-dimer >40 mg/dL); oral steroids without success; bleeding requiring transfusions (hemoglobin 6.1 gm/dL) | Improved size and number of lesions, no further GI bleeding or anemia | 1.6 to 2 mg/m²/day | 5–12 ng/mL       | Less than 1 month; Discontinued sirolimus and at 4 months off therapy: no evidence of microscopic blood in stool and normal hemoglobin levels, stable lesions |
| Wang KL, Ma SF, Pang LY, Zhang MN, Hu LY, Liu MJ, Zou LP [13] | Sirolimus alternative to blood transfusion as a life saver in blue rubber bleb nevus syndrome | *Medicine (Baltimore)*      | 2018         | 12 yo F with multiple hemangiomas on head and neck, limbs and trunk, tip of tongue and digestive tract. Severe anemia, requiring red cell transfusion every 2 weeks. Mutation in exon 15 of TEK gene | Improved hemoglobin, skin and digestive tract hemangiomas, no further transfusions | 1 mg/m³/d, average 0.7 mg/d | 6.2–11.89 μg/L   | 1 month             |
| Kizilocak H, Dikme G, celkan T [14] | Sirolimus experience in blue rubber bleb nevus syndrome                        | *J Pediatr Hematol Oncol*  | 2018         | Four children, ages 4–15 years. Three with GI lesions, one with respiratory tract lesions | Normalized hemoglobin, decreased pain, decreased size of lesions | 1.2 mg/m²/d     | —                | 2 months            |
Abbreviations

BRBNS: blue rubber bleb nevus syndrome
GI: gastrointestinal
mTOR: mammalian target of rapamycin
ISSVA: International Society for the Study of Vascular Anomalies
PI3K: phosphoinositide-3-kinase.

Disclosure

The abstract was presented as a poster at the 2015 ASPHO (American Society of Pediatric Hematology/Oncology) meeting.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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