CASE REPORT

# Blue Rubber Bleb Nevus Syndrome: Promising Response To Sirolimus

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**Background**: Blue rubber bleb nevus syndrome is a rare disease involving venous malformations. **Case characteristics**: We present a 6-year-old female with the syndrome, and consumptive coagulopathy.**Intervention/Outcome**: After management with sirolimus, symptoms resolved. **Message**: Sirolimus may be a valuable option for reducing bleeding complications and cosmetic sequelae for the patients with this syndrome.

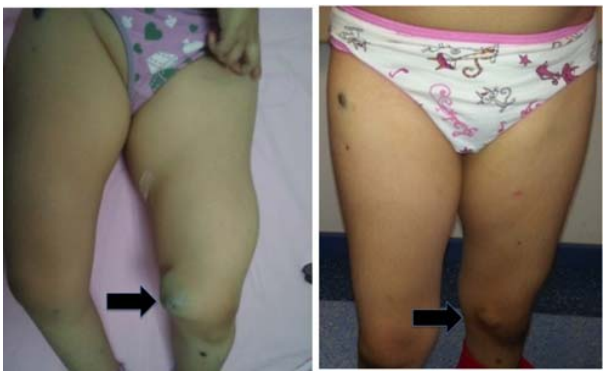
**Keywords**: *Hemangioma, Treatment, Vascular malformations.*

Blue rubber bleb nevus syndrome is a rare disease characterized by venous malformations on the skin, soft tissue and visceral organs, predominantly gastro-intestinal (GI) tract [1]. Skin lesions are multiple soft vascular lesions, which may be papular, nodular or pedunculated, and red or deep blue in color [2]. Medical treatment with steroids, interferon and octreotide has been reported with some success but in most reported patients lesions regrow [3].

Sirolimus is an inhibitor of mammalian target of rapamycin (mTOR) and has been recently used for vascular anomalies with considerable success [4,5]. We report a patient with this syndrome who was unresponsive to steroids and interferon, and was treated successfully with sirolimus.

## Case Report

A 6-year-old female was admitted to our hospital with multiple skin lesions and anemia. The lesions appeared at the age of six months and increased in size and number. Oral steroids were given at a dose of 1 mg/kg/day for few months and sclerotherapy was performed for her largest and painful lesion in the left cervical region without any success. At the age of five she had GI bleeding and colonoscopy showed multiple vascular ectasias and venous malformations. She had been transfused many times in previous year. On admission, she was pale with widespread small variable-sized bluish papules and large vascular masses on the face, mouth, trunk, arms, legs and fingers were noted (***Fig.* 1a**). She had pain in her left knee where the largest vascular lesion was located. Blood tests revealed hemoglobin 6.1g/dL, white blood cell count 8100/mm$^3$, platelets count 77,000/mm$^3$, unconjugated bilirubin 1.6 mg/dL, fibrinogen 104 mg/dL, and D-dimer >40mg/dL. Acanthocytes and schistocytes were noted on perepheral blood smear. The patient was diagnosed as Blue rubber bleb nevus syndrome with typical clinical findings with microangiopathic hemolytic anemia and active consumptive coagulopathy. She also had mild GI bleeding shown with microscopic blood from rectum and fresh frozen plasma and packed red cell transfusions were given. At the end of 11th day, due to no response to medical treatment for anemia and consumptive coagulopathy, sirolimus was started orally at a dose of 1,6 mg/m$^2$/day. Serum sirolimus level was measured weekly and dose adjusted to maintain the therapeutic level between 5-12 ng/mL. Sirolimus level was stabilised at the dose of 2mg/m$^2$/day, but during follow-up daily dose had to be adjusted occasionally. The outcome was assessed by monitoring the reduction in size and color of the lesions. Improvement was noted at day 7, as the size and numbers of lesions were decreased and hematologic findings dramatically improved over days and achieved normal (***Fig.* 1b**). On the 15$^{th}$ day of sirolimus, supportive medications were stopped, her pain resolved and she started walking. The drug was well tolerated and no side effects were seen. She was treated with sirolimus for 17 months. Cutaneous lesions continued to regress during therapy, and no further GI bleeding or anemia was observed. She has been now off-therapy for 4 months without any microscopic blood in stool and normal hemaglobin levels. Her cutaneous lesions are stable and have not progressed since cessation of treatment.



*(a)* *(b)*

**FIG. 1** *Vascular mass on left knee (a); regression of the vascular mass; after eight week of sirolimus treatment (b).*

## DISCUSSION

Blue rubber blub nevus syndrome is heterogeneous in phenotypic expression. The skin lesions arise at birth or early infancy mostly in limbs, trunk and face and vary from bluish black macules or papules to large venous malformations. The size and number of skin lesions tend to increase with age. Visceral lesions can be seen in any sites in the body, but small intestine is the most commonly involved organ. The lesions are fragile and bleed easily. Occult iron deficiency anemia or massive hemorrhage can occur. Bleeding occasionally cause platelet entrapment and consumptive coagulopathy, as in our patient. Cutaneous lesions usually do not require treatment, unless they cause cosmetic or functional problems. The treatment of GI lesions depends on the intensity of bleeding. Occult bleeding and anemia might only need iron supplementation. Massive GI bleeding is the most serious complication of vascular lesions [2,6].

No curative therapy is available for Blue rubber bleb nevus syndrome. Medical treatment including steroids, propranolol and interferon alpha had been reported with variable effect [3]. In almost all cases, lesions regrew to their pretreatment sizes after the treatment was stopped [3]. Our patient demonstrated no response to steroids and interferon previously, however, after sirolimus, was started Hb level stabilized, GI bleeding decreased, and consumptive coagulopathy resolved. No side effect including hyperlipidemia, mucositis, diarrhea, neutropenia, headache, peripheral edema or respiratory distress were observed [4].

Sirolimus has been increasingly used for vascular and lymphatic anomalies and kaposiform hemangioendothelioma [3-5]. Hammill, *et al*. [4] reported 6 cases of venous and lymphatic malformations successfully treated with Sirolimus. We previously reported another patient with giant lymphatic malformation in tongue showing near-total regression after sirolimus [7]. Sirolimus has not yet been demonstrated in clinical trial but is a promising new therapy for a condition not previously medically managed well. Sirolimus should be considered as first-line treatment for treating GI and cutaneous vascular malformations in Blue rubber bleb nevus syndrome.

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