

Sirolimus as a promising drug therapy for blue rubber bleb nevus syndrome: Two-case report

SAGE Open Medical Case Reports
Volume 10: 1–7
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DOI: 10.1177/2050313X221097755
journals.sagepub.com/home/sco



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Abstract

Blue rubber bleb nevus syndrome is a very rare systemic vascular malformation frequently affecting the skin and the gastrointestinal tract. The pathogenesis of the disease is still unclear, and the standard treatment does not exist. This study reports two blue rubber bleb nevus syndrome cases, of which the second patient received the *TEK* gene mutations detection and got a low-dose sirolimus therapy, compared with the first patient who was not treated with sirolimus. The report shows some positive findings of *TEK* gene mutations and the efficacy of sirolimus treatment. We postulate that the *TEK* gene mutations play an important role in the pathogenesis. The mutations of different locations of the *TEK* gene cause a wide range of activating TIE2 mutations, which could stimulate the mammalian target of rapamycin signaling pathways to mediate angiogenesis, resulting in different clinical phenotypes of cutaneomucosal venous malformations. Sirolimus could effectively block the upstream and downstream factors of mammalian target of rapamycin signaling pathways to achieve the antiangiogenic effect. The initial dose of sirolimus can be 0.05–0.1 mg/kg/d for a trough level of 5–15 µg/L in the treatment of blue rubber bleb nevus syndrome. However, a lower-dose sirolimus is also effective while minimizing the side effects.

Keywords

Blue rubber bleb nevus syndrome, *TEK* gene mutations, mTOR, sirolimus

Date received: 31 October 2021; accepted: 13 April 2022

Introduction

Blue rubber bleb nevus syndrome (BRBNS) is a very rare disease, which is characterized by multiple vascular malformations affecting more frequently the skin and the gastrointestinal tract. The symptoms mostly occur at an early age,¹ yet it is easy to be misdiagnosed for its extremely low incidence. The gastrointestinal bleeding and the secondary iron deficiency anemia are the main complications of BRBNS, and these could be fatal without effective treatments.² Most patients need the iron supplement and the blood transfusions along their whole lives.

The pathogenesis of BRBNS is still unclear so far, but the *TEK* gene mutations are thought to be the most persuasive one. Nowadays, there is still no standard treatment for BRBNS. Of note, the effectiveness of sirolimus has been demonstrated by more and more studies, which indicated that sirolimus could be a promising alternative for the disease.

In this report, two patients admitted to our hospital were diagnosed as BRBNS. Both of them had characteristic

clinical manifestations and received adequate diagnostic tests. The differences were that the second case received the *TEK* gene mutations detection and was also applied oral sirolimus therapy, and afterwards achieved a better clinical prognosis.

Case I

A 23-year-old female was admitted to our hospital for multiple congenital purplish nodular lesions on the skin. The

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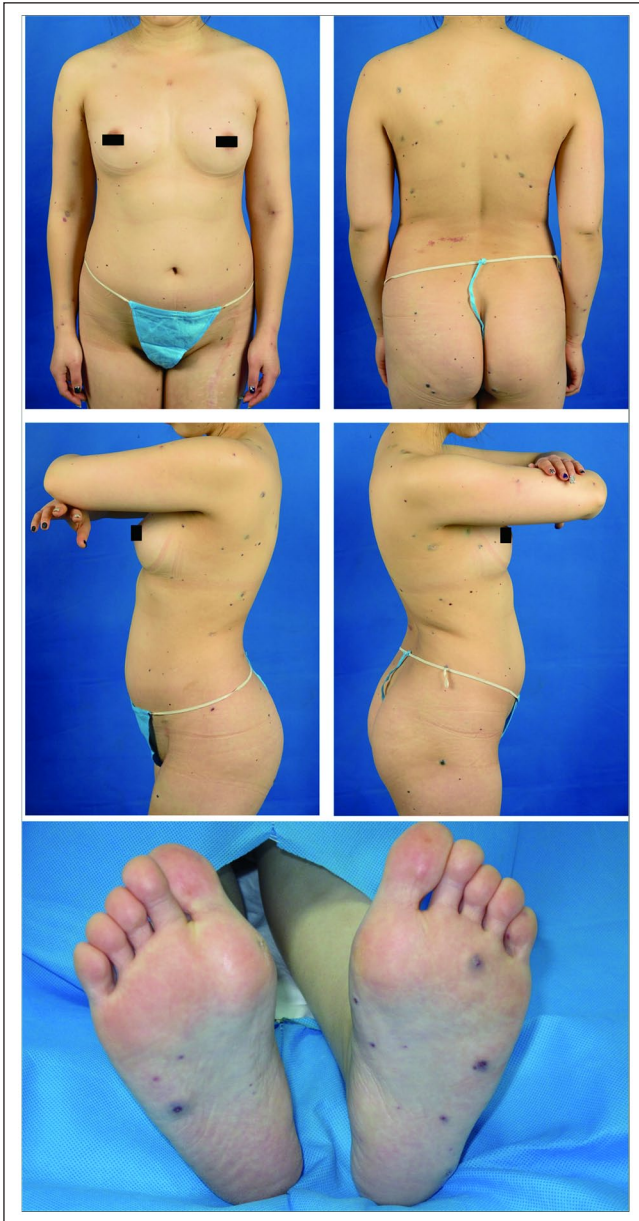


Figure 1. Physical examination of Case 1: Multiple irregular blue-black macules or papules can be seen on her trunk, upper limbs, buttocks, and planta.

lesions manifested gradually for past 23 years with occasional ulcerating and bleeding. She had blood in the stools and anemia for many years. Multiple irregular macules and papules, with a blue-black color, were found on her trunk, upper limbs, buttocks, and planta. These lesions and bumps, with the diameters from 0.3 to 0.6 cm, were easily compressible and could be refilled promptly when the pressure was released (Figure 1). The blood routine test showed a severe anemia (Hb 59.0 g/L) with normal coagulation parameters (international normalization ratio, INR 0.99). The result of biochemical examination was normal. Fecal occult blood was checked three times, and all results were positive. The

esophagogastroduodenoscopy (EGD) revealed multiple bluish vascular lesions within the gastric fundus, gastric body, gastric antrum, duodenal bulb, and descending part of the duodenum (Figure 2). The diameters of the lesions measured from 0.3 to 1.0 cm without active bleeding. The patient was diagnosed as BRBNS. Two units of erythrocyte transfusions were given twice at an interval of 2 weeks. The patient was discharged with the iron supplements for anemia prevention. Three years later, the patient suffered a segmental small-intestine resection from intussusception at another hospital during the follow-up.

Case 2

A 14-year-old female patient complaining of chronic intestinal bleeding was admitted to our hospital. Multiple bluish nodules on her lip, neck, shoulder, and back were observed at birth, which manifested gradually over time. Erythrocyte transfusions had been applied to her many times because of severe anemia. She had been diagnosed as BRBNS at 12-year-old age, and a heterozygous de novo mutation in the *TEK* gene was detected by blood samples sequencing.³ Then the patient received a trial of daily sirolimus therapy for 1 year, and her Hb markedly increased without blood transfusions. However, her non-compliance with taking sirolimus regularly, caused her Hb to drop.

A cyanotic elevated soft vascular lesion was present on the lower lip, measuring 1.5 cm × 2.5 cm, and multiple dark-cyan masses were observed on the back of the neck, cranium, and upper limbs, approximate 3.5 cm in diameter. The masses felt rubbery and could be compressible. There were no ulcers on these lesions (Figure 3).

The blood tests showed moderate anemia (Hb 65.0 g/L) characterized by microcyte and hypopigmentation. The fecal occult blood test was performed three times with positive results. Many dark hyperemia strawberry-like masses in various sizes were found spreading on the esophagus, the entire stomach, the duodenal bulb, and the descending duodenum during the EGD. The colonoscopy detected dozens of violaceous masses spreading along the colon and rectum (Figure 4). In addition, the video capsule endoscopy also revealed multiple dark red masses located in the jejunum and ileum (Figure 5).

The iron supplementation was provided by oral administration of ferrous succinate at a dose of 200 mg, with a frequency of three times a day (TID) for 1 month. And the Hb increased slowly (from 65.0 to 74.0 g/L). Then the iron sucrose injection was applied at a dose of 100 mg, with a frequency of twice a week for 6 weeks. Afterwards, the Hb increased to 84.0 g/L, and the serum iron and the ferritin level were back to normal. A lower-dose sirolimus was prescribed due to an efficacious response in the past. The maintenance dose was 1.2 mg (=1.2 mL)/d, equivalent to 0.025 mg/kg/d, for a target plasma trough level at 1–5 µg/L. The Hb improved from 84.0 to 96.0 g/L after a month of oral

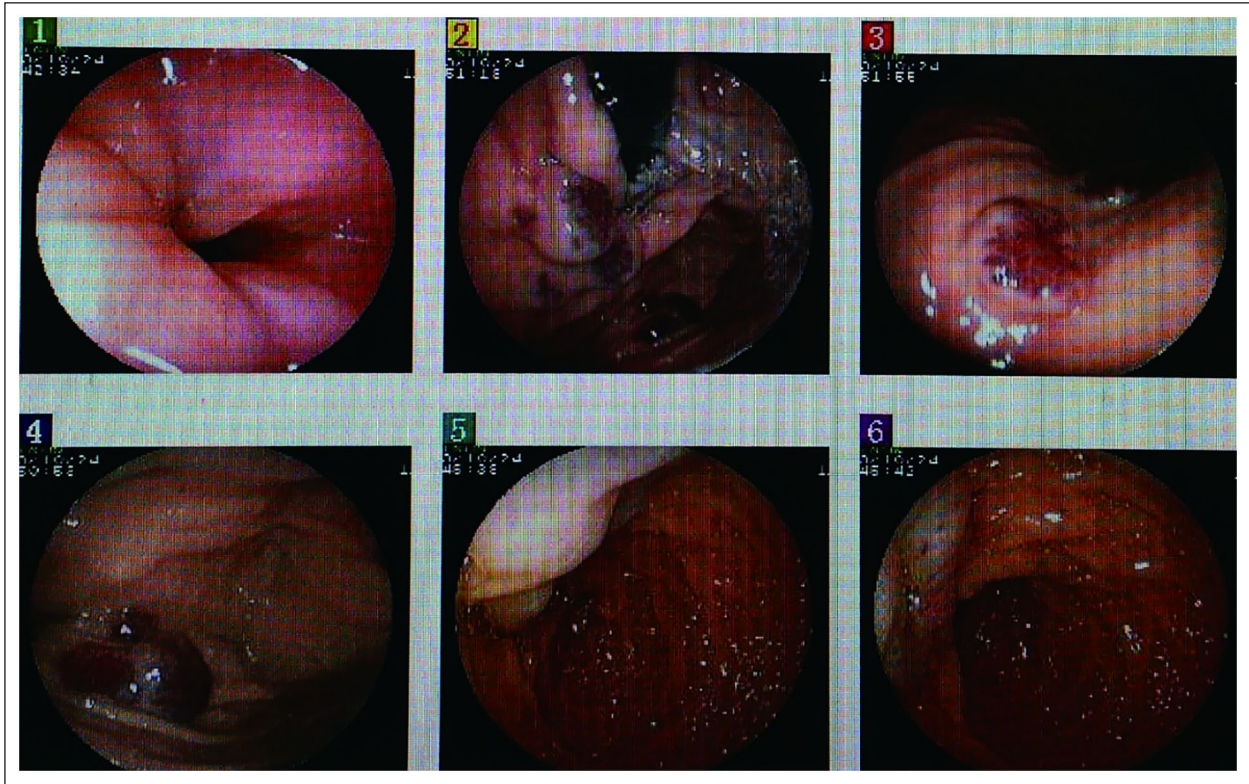


Figure 2. EGD of Case 1: Multiple bluish hemispherical vascular lesions were observed within the gastric fundus, gastric body, gastric antrum, duodenal bulb, and descending part of duodenum. EGD: esophagogastroduodenoscopy.

sirolimus treatment. Then the Hb increased to 121.0 g/L after a 3-month sirolimus treatment, and no adverse drug reactions were observed during the period. The fecal occult blood test was rechecked three times after the sirolimus treatment, and the results were all negative.

Discussion

BRBNS is also known as Bean syndrome, as William Bean first reported the disorder in 1958.⁴ Its predominant pathological feature is congenital venous and lymphatic malformations.⁵ BRBNS is a very rare systemic vascular malformation. The incidence of this syndrome is only 1:14000.⁶ BRBNS is considered as a sporadic disorder;¹ however, a few cases presented a family history of this syndrome.⁷ The pathogenesis of BRBNS is still unclear. It is postulated that the disease is caused by somatic mutations in the *TEK* gene (encoding TIE2, the endothelial cell tyrosine kinase receptor for the angiopoietins) on chromosomal location 9p21, which results in multifocal cutaneomucosal venous malformations. Soblet et al. reported 32 of 35 lesions from 15 of 17 individuals (88.2%) with BRBNS had the *TEK* gene mutations. These mutations were in *TEK* exon 17 and 23. The majority (13 of 15) of BRBNS patients had two somatic mutations on the same allele of the *TEK* gene. The

most frequent mutations (5 of 15) were c. (3314C>A; 3316A>C), which resulted in the amino acid substitution p. (Thr1105Asn; Thr1106Pro) located in the C-terminal tail of TIE2.⁸ Overexpression of the new mutants resulted in ligand-independent hyperphosphorylation of the receptor, which would mediate vascular maturation and angiogenesis. This demonstrated that a wide range of activating TIE2 mutations caused BRBNS. Wouters et al. reported 12 families of inherited cutaneomucosal venous malformations with the *TEK* gene mutations in exon 15 or 17 and 22. The most-frequent mutation (6 of 12) was c.2545C>T, which resulted in the amino acid substitution Arg849Trp located in the tyrosine kinase domain of TIE2.⁹ As for the second case, the *TEK* gene mutation was also identified,³ and her mutation was just the same as the majority of Wouters et al. described. However, the clinical phenotype of the second case was not similar to those reported by Wouters et al., in which 12 of 14 individuals (from six families) did not involve any internal organs. Although the second case showed an autosomal dominant transmission, whether the mutation was spontaneous or inherited from her parents was still unclear because we could not reach to her parents.

BRBNS primarily involves the skin and the digestive tract and may also affect other organs such as central nervous system, liver, muscles, and so on.^{1,7} The skin lesions are



Figure 3. Physical examination of Case 2: A cyanotic elevated soft vascular lesion was present on the lower lip, and multiple darkcyan masses were observed on the back of the neck, cranium, and upper limbs.

characterized by blue or purple, compressible, nodules, or masses, which mostly occur at birth or an early age and may grow in number and size with increasing age.^{1,7,8} As for the digestive tract, the most commonly involved area is the small intestine, followed by the colon and stomach.⁷ The gastrointestinal lesions can cause occult bleeding and the secondary iron deficiency anemia, which are the main clinical manifestations of BRBNS.⁷ The morbidity and mortality are determined by the involved organs and the severity of the lesions.¹ The key points of the diagnosis of BRBNS are the presence of the characteristic skin and gastrointestinal tract lesions. The endoscopic examinations of the digestive tract are essential to support the diagnosis. Especially the capsule endoscopy, with the advantage of non-invasiveness and painless, is the most recommended option.

To date, no guidelines are available for the management of BRBNS. The treatment depends on the locations of lesions and the severity of the disease. All patients with anemia should consider conservative measures like the iron supplementation and the blood transfusions. And both of the two cases received iron oral intake. If the Hb fails to increase

markedly, the active hemorrhage or the iron absorption deficiency due to extensive gastrointestinal lesions should be considered, and the iron supplement applied through injection is recommended like the second case.

Endoscopic interventions, such as band ligation, laser photocoagulation, sclerosing agent injection, or submucosal dissection, have been suggested for the treatment of vascular lesions of digestive tract, and good clinical outcomes have been reported, though without strong evidence to support long-term benefits.^{7,10,11} Moreover, this type of treatment should be applied with caution because the lesions of gastrointestinal tract are occasionally transmural, and the interventions might cause perforations.^{10,12} We did not provide any endoscopic treatments in these two cases because there were no signs of recent active hemorrhage of gastrointestinal lesions.

Severe cases, such as massive hemorrhage or other complications like intestinal rupture, bowel obstruction, intestinal torsion, and intussusception, may require a surgical resection of the involved gastrointestinal lesions.^{2,12–15} The first case received such treatment when the intussusception occurred.



Figure 4. Colonoscopy of Case 2: Dozens of violaceous masses were detected in the colon and rectum.

However, the surgical choice is controversial. It might cause short-bowel syndrome if the lesions are extensive,¹² and it is believed that lesions will recur due to the extensive nature of the venous malformations.^{6,7}

Systemic drugs such as corticosteroids, α -interferon, and octreotide were sometimes used to decrease angiogenesis.^{16,17} However, there was insufficient evidence about the prognosis of these cases. Notably sirolimus, also known as rapamycin, had been demonstrated the effectiveness in the treatment of vascular anomalies such as kaposiform hemangioendothelioma, diffuse microcystic lymphatic malformation, and capillary lymphaticovenous malformation.^{18,19} It is also known as a novel drug to treat BRBNS. The exact mechanism of action of sirolimus in BRBNS remains unclear, but some proposed involved signaling pathways were revealed. The ligand-binding activation of TIE2 receptor could stimulate intracellular signaling pathway phosphatidylinositol-3-kinase (PI3K)/AKT/ mammalian target of rapamycin (mTOR) (downstream of TIE2 mutations) to mediate vascular maturation and angiogenesis, which was common in BRBNS.²⁰ Moreover, the vascular endothelial growth factor (VEGF), a main regulator in angiogenesis, was considered to be both an upstream activator and downstream effector of mTOR.²¹ In addition, a stem cell growth factor receptor (c-kit), acting as a tyrosine kinase upstream of mTOR, was found expressed on the endothelial cells from the small venous of BRBNS lesions.²² Therefore, sirolimus, as an inhibitor of mTOR,

could effectively block the upstream and downstream factors of the mTOR signaling pathways to achieve antiangiogenic effect in the patients with BRBNS.

The first report about the therapeutic benefit of sirolimus for BRBNS was published by Yuksekkaya et al.²³ Afterwards, more reports also demonstrated the effectiveness of sirolimus in the management of gastrointestinal bleeding and reduction of lesions sizes.^{3,7,24–26} It was concluded from previous studies that the initial dose of sirolimus could be 0.05–0.1 mg/kg/d for a target plasma trough level at 5–15 μ g/L in the treatment of BRBNS. Other studies showed that an even lower dose of sirolimus could have a positive effect in the treatment of BRBNS while minimizing the side effects.^{5,27,28} Although poor compliance causing subtherapeutic sirolimus trough levels seemed to lead symptoms relapse.⁷ As for the second case, considering that she had undergone a long-term sirolimus treatment without taking it for a short time, and there was no evidence of overt bleeding in gastrointestinal tract, the patient was treated with a maintenance dosage of sirolimus at 0.025 mg/kg/d for a target plasma trough level at 1–5 μ g/L. Then her Hb increased steadily from 84.0 to 121.0 g/L after a 3-month treatment without any adverse drug effects and complications. And the increase in Hb may be due to a decrease in gastrointestinal occult bleeding, which was revealed by the results of the fecal occult blood tests turning from positive to negative. Based on these findings, it is evident that even a low dose of

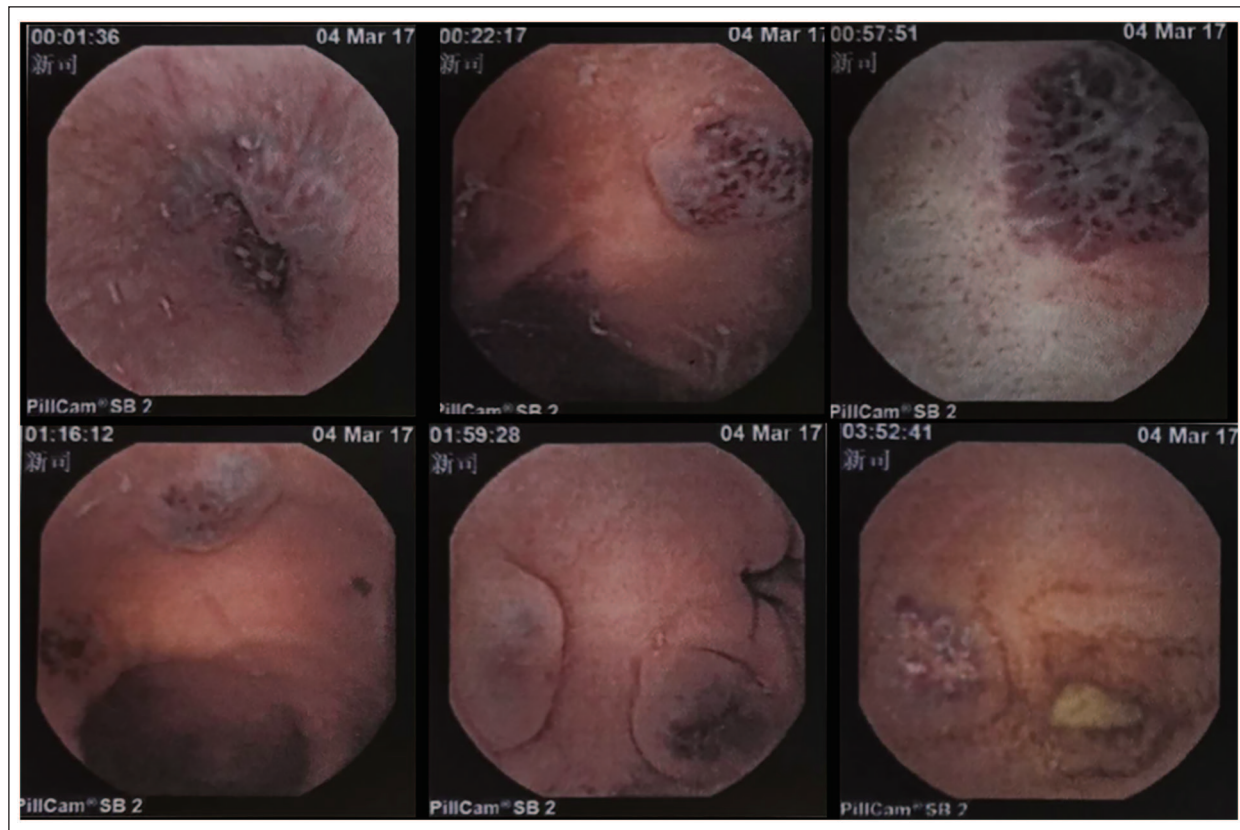


Figure 5. Video capsule endoscopy of Case 2: Multiple dark red masses were observed in the jejunum and ileum.

sirolimus was not only safe but also sufficient in maintaining the normal Hb level, which could effectively prevent the patients from blood transfusions.

Conclusion

An early diagnosis of BRBNS is extremely important because internal lesions may lead to severe hemorrhagic complications. Simultaneous presence of anemia and multiple cutaneous vascular lesions should alert practitioners to the consideration of BRBNS. The endoscopic tests of the digestive tract are important to confirm the diagnosis. The *TEK* gene mutations may be the possible pathogenesis of BRBNS. Sirolimus, an inhibitor of mTOR, can be used as a promising drug therapy for symptomatic BRBNS, in case of fatal complications. But the standard sirolimus treatment, including adequate dosing, target plasma trough level, duration of therapy and long-term side effects, should be determined through further studies.

Acknowledgements

The authors acknowledge our patients and their families who gave us consents to publish the patients' medical condition and share their images with an aim to contribute meaningfully to the medical literature.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent

The written informed consents for publication of the two cases and relevant clinical images in this study have been obtained from the two patients and their parent/legal guardian

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