Bean syndrome in childhood: Use of sirolimus in a severe case

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ABSTRACT

Bean syndrome, also known as blue rubber bleb nevus syndrome, is a rare congenital disorder characterized by multiple venous malformations affecting the skin, soft tissues, and gastrointestinal tract. Its main complication is chronic gastrointestinal bleeding, which can lead to iron-deficiency anemia and a lower quality of life.

We present the case of a pediatric patient diagnosed with Bean syndrome, in whom typical skin lesions and gastrointestinal involvement were identified. We describe the clinical course, the diagnostic tests performed, and the treatment regimen initiated with sirolimus.

This case highlights the importance of recognizing this condition in children for early diagnosis and timely treatment, as well as the need for multidisciplinary follow-up. Sirolimus represents a promising therapeutic option for severe cases, although it requires close monitoring.

Keywords: *Bean syndrome; vascular malformations; gastrointestinal bleeding; sirolimus; pediatrics.*

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INTRODUCTION

Blue rubber bleb nevus syndrome (BRBNS, OMIM 112200), also known as Bean syndrome, is a rare congenital vascular disorder characterized by multiple venous malformations in the skin, mucous membranes, and internal organs, particularly the gastrointestinal tract. First described by Gascoyen[1] and characterized by Bean,[2] BRBNS typically presents with soft, compressible, bluish skin nodules and gastrointestinal lesions that cause chronic bleeding and iron-deficiency anemia.

Fewer than 300 cases have been reported in the literature; since the actual incidence cannot be estimated, the data are heterogeneous and likely underestimated.[3] In some cases, somatic mutations in *TEK/TIE2* have been identified, associated with dysregulated angiogenesis. Management is symptomatic and may include iron supplementation, transfusions, endoscopic or surgical approaches, and, more recently, mTOR (mammalian target of rapamycin) inhibitor therapy such as sirolimus, which has been reported in case series with favorable outcomes.[4-6] Evaluation and treatment should be conducted within multidisciplinary teams and in accordance with international guidelines for vascular anomalies.[7]

CLINICAL CASE

An 8-year-old male patient with a history of resection of a vascular malformation on his left index finger during his first month of life (pathology: venous vascular malformation with giant cell reaction) and amputation of the affected phalanx at 7 months of age due to rapid growth of the lesion. He presented with fatigue and pallor that had persisted for 1 month.

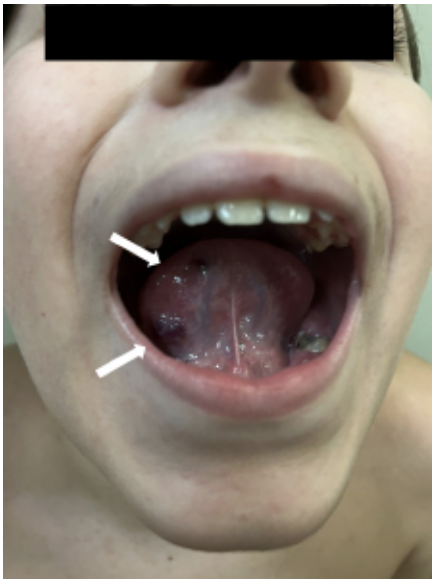
On admission, he was pale, tachycardic, with a 2/6 systolic ejection murmur; he was in cardiorespiratory sufficiency. On examination, multiple bluish, soft, compressible skin nodules with a smooth surface were identified on both feet; in addition, two bluish nodules of similar consistency were found on the tongue (*Figures 1* and *2*). No local murmurs, thrills, or temperature changes were detected in the lesions. Anthropometry: weight Pc 8, height Pc 10, body mass index 14.8 (Pc 18), according to the World Health Organization.

The following initial follow-up tests were performed.

Laboratory:

- Complete blood count revealing severe anemia, with hematological parameters indicative of hypochromic microcytic anemia: white blood cells 5240/mm^3 (neutrophils 62%, lymphocytes 32%), hemoglobin 4.9 g/dL, hematocrit 18.5%, platelets 331 000/mm^3), mean corpuscular volume (MCV) 65.6 fl, mean corpuscular hemoglobin (MCH) 17.4 pg, red blood cell distribution width (RDW) 19.7%. Normal coagulation profile. The iron profile

Figure 1. Oral mucosa lesions



Two soft, compressible bluish nodules (white arrows) are visible on the tongue, consistent with superficial venous malformations. These lesions can affect not only the skin and internal organs but also the mucous membranes.

showed markedly reduced serum iron and ferritin levels, with a transferrin saturation of 2%.

- Weakly positive direct Coombs test; negative serology and antibodies for celiac disease.

The patient reported no significant gastrointestinal symptoms such as dysphagia, vomiting, abdominal pain, weight loss, or bloody stools. He had daily, well-formed bowel movements. An abdominal ultrasound and intestinal Doppler were performed, revealing no significant abnormalities. Upper gastrointestinal videoendoscopy (EGD) and colonoscopy revealed multiple sessile, bluish, submucosal vascular nodules along the gastrointestinal tract (five in the upper tract and five in the lower tract), consistent with venous malformations. Biopsies were not taken due to the risk of bleeding (*Figure 3*).

Upon admission, the patient received a red blood cell transfusion (7 ml/kg), intravenous iron (iron saccharate, 5 doses on alternate days), and oral ferrous sulfate supplementation.

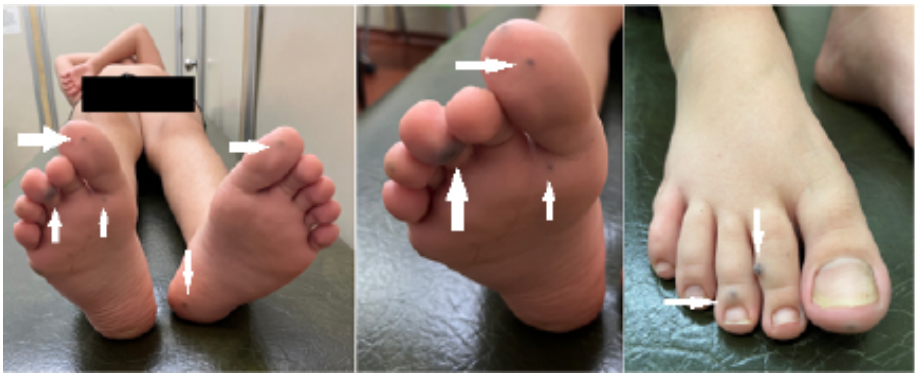
Based on clinical and endoscopic findings, Bean syndrome was diagnosed; there is no confirmation from molecular testing.

Antiangiogenic therapy was initiated with oral sirolimus at 1 mg every 12 hours, and the dose was subsequently adjusted to 1 mg/day based on serum levels, with close clinical monitoring. The patient tolerated the medication well, and after eight months of outpatient follow-up, he showed progressive normalization of hemoglobin levels and no clinical bleeding (*Figure 4*).

DISCUSSION

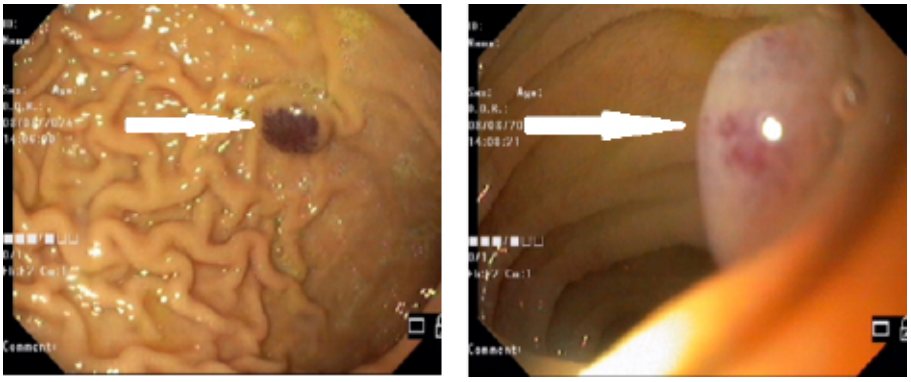
Blue rubber bleb nevus syndrome (BRBNS) is a rare vascular malformation that is a major cause of chronic anemia due to occult bleeding in children, especially when bluish skin nodules are compressible. These nodules are usually present at birth and increase in number and size with age, without regression.[3-6] Gastrointestinal endoscopy should be considered even in the absence of symptoms when clinical suspicion is high,

Figure 2. Lesions in both feet



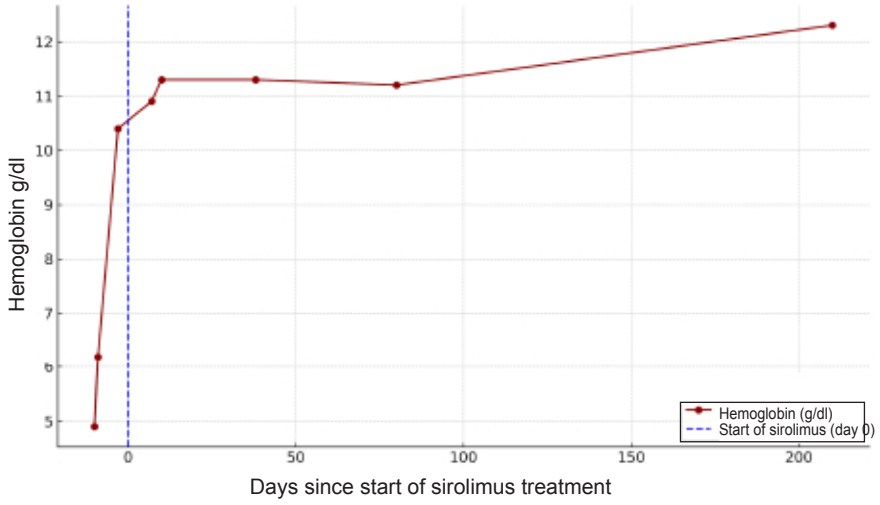
Multiple bluish, soft, and compressible nodules are observed, with a "rubber blister" appearance characteristic of this condition (arrows).

Figure 3. Endoscopic findings



Sessile, submucosal, bluish vascular nodules along the digestive tract are consistent with venous malformations.

Figure 4. Changes in hemoglobin levels before and after treatment with sirolimus



Improvement is observed, with stable hemoglobin levels since treatment started.

given that gastrointestinal involvement (although sometimes asymptomatic) is characteristic and may present with hematemesis, hematochezia, melena, or complications such as volvulus and intestinal infarction.

The differential diagnosis includes other vascular malformations (cavernous hemangiomas, isolated venous malformations), hereditary hemorrhagic telangiectasia, juvenile polyposis, inflammatory bowel disease, and hematologic disorders causing severe anemia. Other affected organs include the liver, spleen, kidneys, brain, lungs, and bladder, with possible manifestations such as hematuria, hemoptysis, hemopericardium, or seizures.

Although the diagnosis is clinical and supported by additional tests, genetic confirmation by screening for *TEK* mutations may be useful in selected cases.[3-5]

The management of these patients requires a specialized interdisciplinary approach, as recommended by the International Society for the Study of Vascular Anomalies (ISSVA),[7] and must be tailored to the individual. Intravenous iron and blood transfusions correct acute anemia; endoscopic therapies or segmental resection are indicated for focal lesions with recurrent bleeding or mechanical complications.

In recent years, sirolimus has demonstrated efficacy in case series and reports in reducing bleeding and lesion size, decreasing the need for transfusions, and improving hemoglobin levels.[4-6] It is an mTOR inhibitor with antiangiogenic and antiproliferative properties. Pediatric doses are typically initiated at 0.8-1 mg/m^2/day and adjusted to achieve target serum levels of 5–10 ng/mL.[4,8] In this case, treatment was initiated at 1 mg every 12 hours and then reduced to 1 mg daily due to elevated plasma levels.

Its use requires close monitoring, including complete blood counts (to assess the risk of thrombocytopenia and leukopenia), lipid profiles, renal function, serum drug levels, and infection surveillance. Monthly evaluations are recommended during the first 3 months, then every 3 months, for monitoring. Trough levels are initially measured every 1-2 weeks until two consecutive measurements are within the target range.[8]

Reports indicate frequent adverse effects that are generally mild (grade 1-2) and self-limiting, such as stomatitis (49-53%), hypercholesterolemia (variable), transient elevations in liver enzymes (18%), cytopenias (variable), and increased susceptibility to infections; the incidence and severity vary across studies.[9-12] The optimal duration of treatment is not defined and should be based on clinical response and the risk-benefit ratio.[13]

This case illustrates the importance of early clinical suspicion of BRBNS in pediatrics and the value of a multidisciplinary approach (pediatrics, gastroenterology, surgery, hematology, and diagnostic imaging) to optimize outcomes for a syndrome that presents multiple clinical challenges. Sirolimus is a promising therapeutic

alternative in severe forms, but its use requires individualized evaluation, informed consent, and rigorous monitoring for potential adverse effects. ■

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