



## Blue Rubber Bleb Naevus Syndrome- A rare cause of microcytic, hypochromic anemia

Authors

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### Abstract

**Introduction:** Blue rubber bleb naevus syndrome, also known as Bean's syndrome, is characterized by multiple vascular malformations involving skin, gastrointestinal tract and other parts of the body. The main clinical presentation is soft, compressible skin lesions along with bleeding from the gastrointestinal tract.

**Case Report:** 24 year old male presented with skin lesions and easy fatiguability since the age of 3-4 years. On examination, there were multiple soft compressible naevi all over the body, and a biopsy from one of these confirmed a squamous epithelium lined vascular lesion. On imaging similar lesions were also noted in the lungs, liver, brain, abdominal wall and in the gut. Colonoscopy revealed vascular lesions in the rectum, sigmoid colon and caecum. The biopsy findings and typical cutaneous and gut lesions allowed for a diagnosis of blue rubber bleb naevus syndrome to be made. The patient was managed conservatively and is following up regularly.

**Conclusion:** Bean's syndrome is rare cause of microcytic anemia. Proper patient counseling and follow up is a must for the well being of the patient.

### Introduction

Blue rubber bleb naevus syndrome (BRBNS), also known as Bean's syndrome is a rare disease characterized by multiple vascular malformations that mainly involve the skin and gastrointestinal tract<sup>(1)</sup>. The presenting complaints may be variable, however, most patients present with iron deficiency anaemia occurring due to bleeding from these malformations present in the gastrointestinal tract<sup>(2)</sup>. Over 200 cases have been reported so far in the literature.

We present a case of 24 year old male who was brought to us with recurrent iron deficiency anemia requiring frequent blood transfusions, with a past history of abdominal surgery done for

intussusception along with lesions of the skin and gastrointestinal tract. We treated our patient conservatively with iron supplementation and blood transfusion and he is on regular follow up.

### Case Report

A 24 year old male presented to us with the complaints of easy fatiguability and multiple bluish skin lesions since the age of 3-4 years. His relatives had first noticed these lesions on his legs, which then gradually progressed over the trunk, upper limbs, scalp and face and slowly increased in size. Despite treatment, new lesions continued to appear. Patient also gave history of melena, however there was no history of hematemesis or

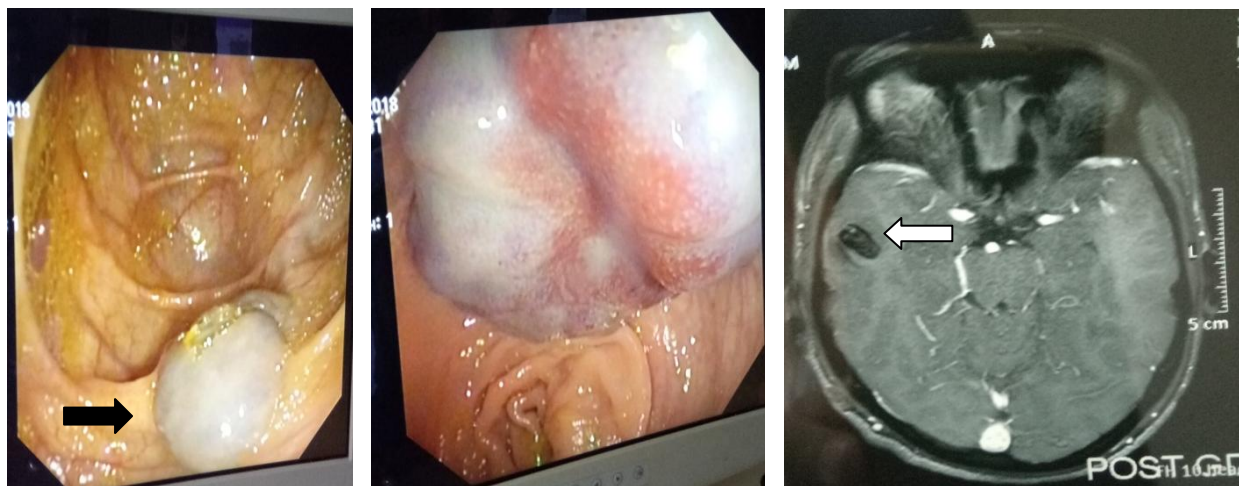
frank rectal bleeding. He had also received multiple blood transfusions over the years. 4 years back he had history of sudden onset severe pain abdomen and multiple episodes of vomiting, for which he was admitted at a hospital and was diagnosed to have intussusception and operated for the same. However, details regarding the nature of surgical procedure or a biopsy report were unavailable. Despite the surgery, he continued to have melena along with the need for blood transfusions. He was born out of a non-consanguineous marriage with no family history of similar illness. On presentation to our hospital, the patient was pale. There were multiple compressible bluish lesions over the scalp, face, arms, trunk and lower limbs ranging from 1-1.5 cm in size. The overlying skin was smooth; lesions were soft, non-tender and reappeared after removing the pressure. There were abdominal scars of previous surgery along with a palpable spleen. Rest of the examination was unremarkable.

Laboratory investigations were suggestive of anaemia (Hb- 7.5 g/dl) of microcytic, hypochromic type. Serum iron and ferritin were low. Stool for occult blood was positive. Ultrasound abdomen showed an enlarged spleen

with multiple hypoechoic lesions in right upper quadrant and right iliac fossa adjacent to bowel loops and probably intrabowel in location. Multiple vascular channels were noted in left lumbar region, however, vascularity could not be detected by Doppler due to no/slow flow. One of the skin lesions of the left lumbar region showed vascular channels with arterial flow suggestive of arterio-venous malformation. Few others did not show arterial flow probably suggestive of venous malformations. Contrast enhanced CT abdomen with oral and rectal contrast showed suspicious polypoid thickening at the posterior wall of rectum, hepatic flexure of the colon and descending colon. In addition, there was an ill defined mixed lytic sclerotic lesion in the right iliac bone. CT Enterography showed similar findings with lesions also seen in the small bowel and subcutaneous tissues of the abdomen. Multiple arterial enhancing lesions were also seen in liver and both lungs. MRI Brain was done to look for lesions in central nervous system and it showed a well defined intra-axial heterogeneous lesion in the right temporal lobe showing popcorn appearance, surrounded by rim of hemosiderin and blooming on GRE images, suggestive of cavernoma.



**Figure 1-** Bluish vascular lesions seen on the hard palate, back and forearm



**Figure 2-** Colonoscopy images showing vascular lesions seen in the caecum (left), rectum (centre) and cavernoma as seen on MRI Brain (right)

Upper GI Endoscopy showed antral gastritis. Lower GI Study showed multiple large bluish colored lesions of size >2 cm in rectum, sigmoid colon and caecum, however biopsy was deferred due to the vascular nature of the lesions. Biopsy of one of the lesions on the forearm showed keratinized stratified squamous epithelium with underlying subcutaneous tissue showing large, irregular spaces and dilated blood vessels with RBCs and few congested capillaries with focally extravasated RBCs and fibrinoid material, consistent with the diagnosis of BRBNS.

### Discussion

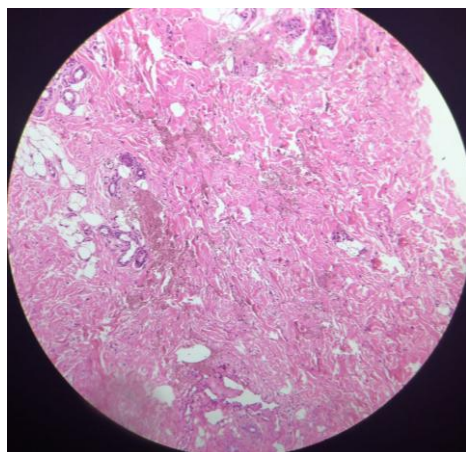
The first full description of hemangiomas of skin with lesions in gastrointestinal tract was provided by W.B. Bean <sup>(1)</sup> in the year 1958, who used the term 'blue rubber bleb naevus' for the characteristic lesions. Today, maximum literature about this condition is found in the form of case reports. The disease usually starts in the form of asymptomatic skin lesions, which are venous malformations that may be present at birth or appear in early childhood <sup>(3)</sup> as in our case. The involvement of the other organ systems occurs later. The exact pathogenesis of the disease is not yet clear. Usually, its occurrence is considered to be sporadic and probably due to somatic cell mutations <sup>(4)</sup>, however, at the same time studies have also reported autosomal dominant pattern of inheritance in cases that were familial <sup>(5)</sup>, linked to

the short arm of chromosome 9 (9p). Somatic mutations in the TEK gene which encodes TIE2 was reported by Soblet et al in patients of blue rubber bleb naevus syndrome <sup>(6)</sup>.

The clinical features depend on the organ of involvement. The skin lesions were originally classified into three types by Bean; soft, bluish, easily compressible and rapidly refilling lesions that appear like blood filled blebs; large cavernous lesions compressing vital structures or causing disfigurement and bluish macular lesions occurring all over the body <sup>(1)</sup>. The lesions seen in our patient were the typical bluish ones described in the first category. The lesions are generally painless and asymptomatic; pain may occur due to contraction of muscle fibres that surround the angiomas <sup>(7)</sup>. The hemangiomas in the gastrointestinal tract can occur from anywhere between mouth to anus <sup>(8)</sup>, our patient had lesions on the hard palate, small and large bowel up to the rectum. The most common mode of presentation of the GI lesions is bleeding leading to iron deficiency anaemia <sup>(2)</sup>, however, there may also be complications like gangrene, intestinal rupture, torsion, volvulus and intussusception <sup>(9)</sup>. The skin lesions are less likely to bleed than the gastrointestinal malformations, and apart from occult blood loss in stools there may also be severe lower GI tract bleeding necessitating blood transfusion <sup>(10)</sup>. The other sites where these vascular malformations can occur include the central nervous system, liver, spleen,



muscles, lungs, orbit, kidneys and pancreas <sup>(11)</sup>. Rare complications include disseminated intravascular coagulation and thrombocytopenia <sup>(11)</sup>.



**Figure 3-** Biopsy of skin lesion showing dilated blood vessels with RBCs in the subcutaneous tissue

A diagnosis of BRBNS is suspected when patient presents with vascular skin lesions that are soft and compressible, along with presence of similar lesions in the gastrointestinal tract and possibly other areas of the body. Histopathology of the vascular lesions reveals ectatic vessels filled with blood, which are lined by single layered endothelium. There are irregular cavernous spaces with presence of smooth muscle fibres in walls of the vessels <sup>(12)</sup>. Upper and lower GI endoscopic studies form an important tool for the diagnosis of vascular malformations in the gut, and can also help in localizing the culprit lesion in case of GI bleed. Sometimes, the lesions may not be seen on conventional endoscopy and newer techniques like CT Enterography, MRI, double balloon enteroscopy or a capsule endoscopy may be required for diagnosis <sup>(10)</sup>. <sup>99m</sup>Tc-labeled RBC scan has also been used to detect the sites of GI bleeding <sup>(13)</sup>. Similarly, magnetic resonance or CT imaging of the other organ systems like lungs and central nervous system may be required depending upon the mode of presentation.

Differential Diagnoses for BRBNS include Osler Weber Rendu disease, Klippel-Trénaunay-Weber and Maffucci syndrome. Osler Weber Rendu disease or hereditary hemorrhagic telangiectasia is

characterized by cutaneous and visceral lesions that may resemble those of BRBNS. However, these lesions are smaller (2-5 mm), punctiform and there is presence of telangiectasias with subungual and nail bed involvement with family history of the disease that helps in differentiating it from BRBNS. Maffucci's syndrome in addition to the skin and visceral lesions has bony abnormalities and defective ossification, while Klippel-Trénaunay-Weber syndrome shows varicosities with hypertrophy of soft and bony tissues <sup>(12,14-15)</sup>. Other differentials to be considered include von Hippel- Lindau disease, Sturge Weber syndrome and hereditary hemorrhagic telangiectasia. Vasculitis syndromes can also have both cutaneous and gastrointestinal manifestations. Similarly, polyposis syndromes like Gardner's (also having lipomas, epidermoid cysts and desmoid tumours), Peutz-Jeghers syndrome (with melanotic macules on mucosae) and Cowden's disease are also important differentials <sup>(12)</sup>.

The skin lesions usually do not require treatment unless they are prone to trauma or are present at joints, or for cosmetic reasons. Treatment may be in the form of surgical removal, sclerotherapy or laser photocoagulation <sup>(7)</sup>. Proper management of the gastrointestinal manifestations forms the backbone of treatment. If there is no major or continuous bleeding, patient may be managed conservatively via packed cell transfusion and supplementation of iron <sup>(15)</sup>. However, due to the nature of the disease in such cases patient will require lifelong iron and/or blood products substitution, which is expensive and compromises the quality of life. Therefore some authorities advocate early surgical treatment before severe bleeding or other complications occur. In life threatening situations, surgery is often the only choice <sup>(5)</sup>. Also, in recent reports, wedge or segmental surgical resection of the small intestine has proved to be safe with sustained clinical remission <sup>(16)</sup>. Overall, two important conditions need to be fulfilled for surgical treatment as a primary choice, the number and extent of the GI

lesions must be known and they should be localized. If lesions are too extensive, excessive bowel resection will lead to short bowel syndrome. Capsule endoscopy can be useful in such cases to determine the extent and number of lesions<sup>(5)</sup>. The procedures that can be used for limited lesions include endoscopic argon plasma coagulation, band ligation, sclerotherapy, and electrocauterization<sup>(5,7)</sup>. However, in case of active bleed the culprit vessel may not be visible and these procedures may fail. Also, the use of these procedures in the relatively thin walled gut may cause perforation or bleeding<sup>(17)</sup>. Other medical modalities of treatment that have been or are used in this condition include anti-angiogenic substances, propranolol, corticosteroids and interferon- $\alpha$ <sup>(10)</sup>. A new method that has been introduced is the use of low dose Sirolimus, which is an anti-angiogenic agent. It was successfully used in an 8 year old girl with severe gastrointestinal bleeding with significant reduction in the vascular lesions and minimal adverse reactions following treatment<sup>(18)</sup>.

For lesions in other areas of the body, the aim is to prevent bleeding or compression of vital structures, in which case surgical resection may be required. The long term prognosis ultimately depends on the number and extent of organ system involvement, the chief among these being the GI tract. Generally the patients can have a good life expectancy, however the quality of life is reduced to recurrent GI bleeding, anaemia, requirement of frequent blood transfusion, long term drug therapy and in some cases, surgery.

### Conclusion

BRBNS forms a rare cause of gastrointestinal bleed leading to microcytic, hypochromic anemia. The treating physician should diligently search for manifestations of this disease in all affected systems. Proper counseling and regular follow up will go a long way in improving the well being and quality of life of the patient.

**Conflicts of interest:** None

### References

1. Bean WB: Blue rubber-bleb nevi of the skin and gastrointestinal tract; in Bean WB (ed): Vascular Spiders and Related Lesions of the Skin. Springfield, Charles C. Thomas, 1958, pp 17–185
2. Seung- Hwan Shin, Hiun- Suk Chae, Jeong-Seon, Hyung-Keun Kim, Young-Seok Cho, Eun-Deok Chang, Kyu-Yong Choi. A case of blue rubber bleb nevus syndrome. The Korean Journal of Internal Medicine: 23:208-212, 2008
3. A Singal, S Vohra, R Sharma And \* S Bhat.t Blue Rubber Bleb Nevus Syndrome with Musculo-skeletal Involvement and Pulmonary Stenosis Indian Pediatr 2016;53: 525-527
4. J.I. Chung\*, H.Alvarez, P. Lasjaunias. Multifocal Cerebral Venous Malformations and Associated Developmental Venous Anomalies in a Case of Blue Rubber Bleb Nevus Syndrome Interventional Neuroradiology 9: 169-176, 2003
5. Kang Kook Choi, Jin Yong Kim<sup>1</sup>, Min Jung Kim, Hyojun Park, Dong Wook Choi, Seong Ho Choi, Jin Seok Heo. Radical resection of intestinal blue rubber bleb nevus Syndrome J Korean Surg Soc 2012;83:316-320
6. Julie Soblet, Jaakko Kangas, Marjut Na'tynki, Antonella Mendola, Raphael Helaers, Melanie Uebelhoer, Mika Kaakinen, Maria Cordisco, Anne Domp martin, Odile Enjolras, Simon Holden, Alan D. Irvine, Loshan Kangesu, Christine Le'aute'-Labre`ze, Agustina Lanoel, Zerina Lokmic, Saskia Maas, Maeve A. McAleer, Anthony Penington, Paul Rieu, Samira Syed, Carine van der Vleuten, Rosemarie Watson, Steven J. Fishman, John B. Mulliken, Lauri Eklund, Nisha Limaye, Laurence M. Boonand Miikka Vikkula. Blue Rubber Bleb Nevus (BRBN) Syndrome Is Caused by Somatic TEK (TIE2) Mutations. Journal of

- Investigative Dermatology (2017) 137, 207e216.
7. Dieckmann K, Maurage C, Faure N, Margulies A, Lorette G, Rudler J, Rolland JC. Combined laser-steroid therapy in blue rubber bleb nevus syndrome: case report and review of the literature. *Eur J Pediatr Surg* 1994; 4: 372-374
  8. Dwivedi M, Misra SP. Blue rubber bleb nevus syndrome causing upper GI hemorrhage: a novel management approach and review. *Gastrointest Endosc* 2002; 55: 943-946
  9. Barlas A, Avsar E, Bozbas A, Yegen C. Role of capsule endoscopy in blue rubber bleb nevus syndrome. *Can J Surg* 2008; 51: E119-E120
  10. Carlos Augusto Real Martinez, Murilo Rocha Rodrigues, Daniela Tiemi Sato, Paulo Pedroso Silveira Júnior, Rafael Fernandes Gama, Christian BorniaMattavelli, and José Aires Pereira. Blue Rubber Bleb Nevus Syndrome as a Cause of Lower Digestive Bleeding. Hindawi Publishing Corporation Case Reports in Surgery Volume 2014, Article ID 683684, 4 pages
  11. Jin XL, Wang ZH, Xiao XB, Huang LS, Zhao XY. Blue rubber bleb nevus syndrome: A case report and literature review. *World J Gastroenterol* 2014; 20(45): 17254-17259
  12. J.J. Oosterheert, M.T. Bousema, J. Lagendijk, M.H.H. Kramer The blue rubber bleb nevus syndrome co-existing with celiac disease *Neth J Med*. 2006 Dec;64(11):431-4
  13. Soo Jin Lee & Ho-Young Lee & Kyuwhan Jung & Sang Eun Kim 99m.Tc-Labeled RBC Scan in a Patient with Blue Rubber Bleb Nevus Syndrome: A Case Report. *Nucl Med Mol Imaging* (2013) 47:115–118
  14. Paller AS. Vascular disorders. *Dermatol Clin* 1987;5:239-50.
  15. Arguedas MR, Shore G, Wilcox CM. Congenital vascular lesions of the gastrointestinal tract: blue rubber bleb nevus and Klippel-Trenaunay syndromes. *South Med J* 2001;94(4):405-10.
  16. Kopacova M, Tachecí I, Koudelka J, Kralova M, Rejchrt S, Bures J. A new approach to blue rubber bleb nevus syndrome: the role of capsule endoscopy and intra-operative enteroscopy. *Pediatr Surg Int* 2007;23:693-7.
  17. Ng WT, Wong YT. Blue rubber bleb nevus syndrome: more lessons to be learnt. *Eur J Pediatr Surg* 2007;17:221-2.
  18. Yuksekkaya H, Ozbek O, Keser M, Toy H. Blue rubber bleb nevus syndrome: successful treatment with sirolimus. *Pediatrics* 2012; 129: e1080-e1084