

Endoscopic and Surgical Management of Blue Rubber Bleb Nevus Syndrome

Zoilo K. Suarez, MD¹, Daniel Castaneda, MD^{2,3}, Adalberto Gonzalez, MD², Fernando J. Castro, MD², and Tolga Erim, DO²

¹Internal Medicine Department, Florida Atlantic University Charles E. Schmidt College of Medicine, Boca Raton, FL

²Digestive Disease Institute, Cleveland Clinic Florida, Weston, FL

³Gastroenterology Department, Annie Penn Hospital, Reidsville, NC

ABSTRACT

Blue rubber bleb nevus syndrome is a rare congenital sporadic disorder characterized by multiple venous malformations localized in the skin, gastrointestinal tract, and internal organs. Gastrointestinal lesions tend to lead to massive or occult bleeding and iron deficiency anemia. The treatment of symptomatic gastrointestinal venous malformations remains a challenge, especially in the setting of recurrent blood loss anemia. An endoscopic approach may be required for refractory cases. We present a case of a 20-year-old patient with blue rubber bleb nevus syndrome with multiple lesions in the stomach, duodenal bulb, small bowel, sigmoid, and descending colon who underwent successful endoscopic mucosal resection, hybrid endoscopic submucosal dissection, and surgical transmural resection of vascular lesions for recurrent bleeding.

INTRODUCTION

Blue rubber bleb nevus syndrome (BRBNS) is a rare congenital sporadic disorder characterized by multiple venous malformations localized in the skin, soft tissues, gastrointestinal tract, which often increase in number and size with age. Autosomal dominant inheritance associated with chromosome 9p has been reported, and somatic activating mutations on the TEK gene encoding an endothelial cell tyrosine kinase receptor for angiopoietins have been found to be part of the disease pathogenesis. The cutaneous lesions are generally present at birth and



Figure 1. Multiple blue rubber bleb lesions present in small bowel—capsule endoscopy image.

tend to be small and localized while gastrointestinal lesions usually are located in the small intestine, followed by the colon and stomach presenting with iron deficiency anemia. Other potential complications of BRBNS include volvulus, intussusception, and necrosis of the intestinal mucosa. We present the case of a patient with BRBNS who underwent successful endoscopic mucosal resection (EMR), hybrid endoscopic submucosal dissection (hybrid ESD), and surgical transmural resection of multiorgan vascular lesions for recurrent anemia management.

CASE REPORT

A 20-year-old man with a history of BRBNS presented to our clinic for evaluation of severe anemia and positive fecal occult

blood in the stool. He was initially diagnosed in the Boston Children's Hospital at the age of 4 years when he underwent surgical resection of a large vascular lesion in his upper back. He was asymptomatic for years but was admitted to our hospital with lightheadedness and weakness and found to have a hemoglobin of 1.7 g/dL and mean corpuscular volume 66. The patient denied any overt clinical bleeding. Physical examination showed multiple blue nevi in the palms and soles, lower extremities, and upper back. Other studies included ferritin 2.0 ng/mL and iron 16 μ g/dL. He was transfused several units of packed red blood cells and was discharged from the hospital on oral iron supplementation.

The patient underwent initial diagnostic esophagogastroduodenoscopy and colonoscopy after this hospital admission revealing

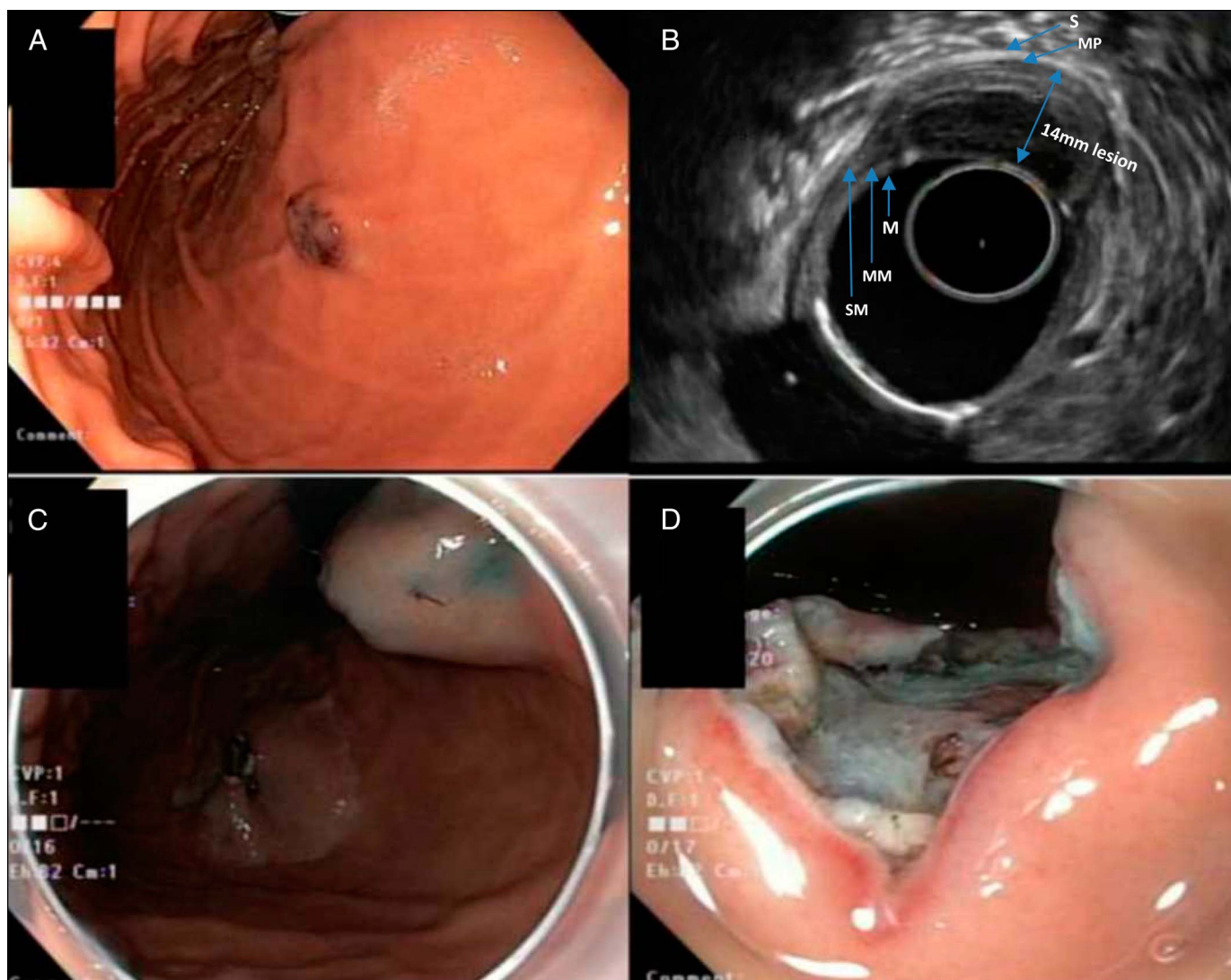


Figure 2. A 14 mm blue rubber nevus lesion in the lesser curvature of the stomach (A). The lesion was found to involve the submucosa (third layer, labeled as SM), but not involving the serosa (labeled S) (B). Other layers labeled in the photograph include M, MM, and MP. The lesion underwent hybrid endoscopic submucosal resection: Adequate lifting of the lesion was obtained with injection of 3 mL of a combination of methylene blue-hetastarch (C). With the use of a 2.8 mm DualKnife electrosurgical knife, markings of the borders of the lesion were performed, followed by careful partial dissection of the lesion. Given the absence of any significant bleeding or deep layer involvement on endoscopic inspection, complete *en bloc* resection was achieved with a 20 mm cold snare. Successful resection of the lesion was achieved with hybrid endoscopic submucosal dissection, without residual tissue and adequate margins (D). M, mucosa; MM, muscularis mucosa; MP, muscularis propria.

multiple blue/purple vascular-appearing nodules with the following distribution: a 8 mm nodule in the gastric fundus, a 10 mm nodule in the anterior gastric wall, a 14 mm nodule in the lesser curvature of the gastric body, a 4 mm nodule on the greater curvature of the distal gastric body, a 15 mm nodule in the duodenal bulb past the pylorus, and three 6- to 8-mm nodules in the sigmoid and descending colon. A video capsule endoscopy revealed 8 nonbleeding blue rubber bleb lesions in the small bowel, which were located predominantly in the proximal small bowel (Figure 1).

Decision was made to endoscopically resect the lesions in the stomach and colon. An initial endoscopic ultrasound was performed to evaluate the gastric lesions because of concern of transmural involvement given their size, but the lesions were found to arise from the submucosa. Through a combination of methylene blue-hetastarch injection for lifting and snare resection with a 1.5 cm Cook AcuSnare (ENDO CUT Q-3), removal of the gastric and colon lesions was achieved successfully by EMR. The 14 mm lesion in the lesser curvature required a hybrid ESD approach for resection (Figure 2) given the size of the lesion without deep submucosal involvement. The hybrid ESD approach allowed *en bloc* resection with minimal intraprocedural bleeding. Hemostasis for transient bleeding was achieved with the use of hot biopsy forceps and hemostatic clips. The procedure was performed in the outpatient setting, and the patient was discharged home the same day on omeprazole 40 mg twice a day for 2 weeks. The pathology specimens showed vascular telangiectasias, consistent with BRBNS.

In the subsequent 2 months, the patient presented with recurrent anemia despite oral iron intake, for which he was started on intravenous iron supplementation. Given the concern for possible transmural involvement, the patient underwent diagnostic laparoscopy. Eleven transmural lesions between 0.5 and 2 cm were found in the small bowel inspection (Figure 3). The 15 mm lesion previously found in the duodenum was removed with an excisional biopsy, and an intraoperative endoscopy was performed for the placement of 2 hemostatic clips at the site after surgical closure. The remaining 10 small bowel lesions were removed surgically with end-to-end anastomosis. The patient recovered well from the procedure and was discharged from the hospital after 4 days. On discharge, the patient's hemoglobin was 10.8 g/dL and mean corpuscular volume 78.9. On follow up 7 months after this intervention, the patient has been asymptomatic and has not required any further transfusion or hospitalizations because of BRBNS complications.

DISCUSSION

BRBNS is a complex multisystemic disorder that can lead to significant morbidity in patients when presenting with overt gastrointestinal bleeding or refractory iron deficiency anemia, as in our case. In general, the management is mainly supportive

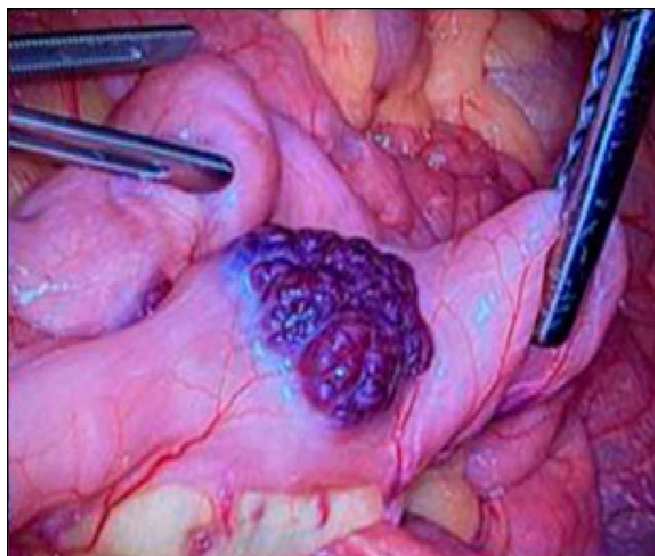


Figure 3. Laparoscopic photographs showing transmural blue rubber bleb involvement in different segments of the small bowel.

with iron supplementation or blood transfusions as needed to correct the anemia.¹ Recently, sirolimus has been studied in pediatric populations leading to a reduction in vascular lesion size, subsequently leading to a decrease in the severity of blood losses and need for transfusion dependence.² Nevertheless, if this approach is unsuccessful, an endoscopic, surgical, or combined approach (ie, laparotomy with intraoperative endoscopy³) can be required. For a primary endoscopic intervention, different techniques have been described in case reports, including the use of a detachable snare,⁴ submucosal dissection,⁵ sclerotherapy,⁶ argon plasma coagulation,⁷ and EMR.⁸⁻¹⁰ In our experience, the application of multiple techniques including EMR, hybrid ESD, and laparoscopy led to clinical success. Owing to the paucity of cases reported in the literature, the management of these vascular lesions can vary, sparing the patient from multiple surgical resections when possible.

According to Jin et al,¹¹ the optimal approach for refractory cases should be chosen based on the extent of intestinal involvement and severity of disease. Adequate endoscopic identification of the lesions is crucial for this purpose, with characterization of the type (multilobulated, nodular, sessile, pedunculated, or ulcerated), continuity, and depth of the lesions.¹² Endoscopic ultrasound can help identify the depth of involvement before endoscopic therapy and could be considered for large lesions because there is a likelihood of transmural involvement, especially in small bowel lesions because of bowel wall thickness. Isolated therapeutic endoscopic techniques should be preferred for mucosal and submucosal lesions because of less invasiveness and postprocedure complications, but in the presence of transmural lesions, EMR or band ligation should be deferred because of the risk of perforation, and a combined approach should be sought. Importantly, case discussion with an experienced laparoscopic surgeon is warranted when approaching

these cases because the presence of transmural nevi involvement will likely require surgical backup.

The evaluation of patients with BRBNS presenting with iron deficiency anemia without overt gastrointestinal bleeding should start with upper and lower endoscopic investigations. However, given that the nevi are more frequently located in the small bowel, if the patients present with persistent anemia after endoscopic therapy, further investigations are warranted as depicted in our case. Cross-sectional imaging with computed tomography/magnetic resonance enterography can be helpful for presurgical assessment, but flat/purely mucosal or submucosal lesions could be missed with these methods while there is a higher likelihood to detect these nevi with the use of video capsule endoscopy.¹³ Although patients with BRBNS can present intussusception, the overall occurrence of intussusception is rare,¹⁴ and no reports of capsule endoscopy obstruction have been reported. We consider clinicians could choose to perform a patency capsule or cross-sectional abdominal imaging before video capsule endoscopy if large lesions have been observed in endoscopic evaluation or the patient had previous episodes of unexplained obstructive gastrointestinal symptoms.

In summary, the implementation of endoscopic resection and surgical approach led to an effective treatment of multiple gastrointestinal vascular malformations, including transmural lesions. Evaluation by a multidisciplinary team including a gastroenterologist, abdominal surgeon, and vascular medicine is the cornerstone for comprehensive care.

DISCLOSURES

Author contributions: ZK Suarez, D. Castaneda, and A. Gonzalez collaborated in the data collection, literature search, and manuscript elaboration. FJ Castro and T. Erim collaborated in the manuscript and interpretation and critical revision of the manuscript for important intellectual content. T. Erim is the article guarantor.

Financial disclosure: None to report.

Informed consent was obtained for this case report.

Received October 20, 2021; Accepted September 2, 2022

REFERENCES

1. Isoldi S, Belsha D, Yeop I, et al. Blue rubber bleb nevus syndrome. Diagnosis and management of children with blue rubber bleb nevus syndrome: A multi-center case series. *Dig Liver Dis.* 2019;51(11):1537–46.
2. Zhou J, Zhao Z, Sun T, et al. Efficacy and safety of sirolimus for blue rubber bleb nevus syndrome. *Am J Gastroenterol.* 2021;116(5):1044–52.
3. Arena M, Virdis M, Morandi E, et al. Blue rubber bleb nevus syndrome: Combined surgical and endoscopic treatment. *Endoscopy.* 2015;47(Suppl 1):E372–3.
4. Wu C, Luo R, Li X, et al. Endoscopic management of blue rubber bleb nevus syndrome in the colon with hemostatic clamp and snare. *Endoscopy.* 2017; 49(6):E149–50.
5. Chen W, Chen H, Shan G, et al. Blue rubber bleb nevus syndrome. *Medicine (Baltimore).* 2017;96(33):e7792.
6. Marakhouski K, Sharafanovich E, Kolbik U, et al. Endoscopic treatment of blue rubber bleb nevus syndrome in a 4-year-old girl with long-term follow-up: A case report. *World J Gastrointest Endosc.* 2021;13(3):90–6.
7. Ng EKW, Cheung FKY, Chiu PWY. Blue rubber bleb nevus syndrome: Treatment of multiple gastrointestinal hemangiomas with argon plasma coagulator. *Dig Endosc.* 2009;21(1):40–2.
8. Xu Y, Wu Y, Dai Z, et al. A combination of single-balloon enteroscopy-assisted laparoscopy and endoscopic mucosal resection for treating gastrointestinal venous malformations in blue rubber bleb nevus syndrome: A case report. *BMC Gastroenterol.* 2020;20(1):182.
9. Rubio-Mateos J, Tojo-González R, Pérez-Cuadrado-Robles E. Endoscopic mucosal resection by double-balloon enteroscopy can be an alternative in small bowel venous malformations. *Dig Endosc.* 2018;30(6):789.
10. Moghadam AD, Bagheri M, Eslami P, et al. Blue rubber bleb nevus syndrome because of 12 years of iron deficiency anemia in a patient by double balloon enteroscopy; a case report and review of literature. *Middle East J Dig Dis.* 2021;13(2):153–9.
11. Jin XL, Wang ZH, Xiao XB, et al. Blue rubber bleb nevus syndrome: A case report and literature review. *World J Gastroenterol.* 2014;20(45):17254–9.
12. Kopáková M, Tachecí I, Koudelka J, et al. A new approach to blue rubber bleb nevus syndrome: The role of capsule endoscopy and intra-operative enteroscopy. *Pediatr Surg Int.* 2007;23(7):693–7.
13. Hu Z, Lin X, Zhong J, et al. Blue rubber bleb nevus syndrome with the complication of intussusception: A case report and literature review. *Medicine (Baltimore).* 2020;99:28:e21199.
14. Xia H, Wu J, Huang Y. Blue rubber bleb nevus syndrome: A single-center case series in 12 years. *Transl Pediatr.* 2021;10(11):2960–71.

Copyright: © 2022 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of The American College of Gastroenterology. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.