Diagnosis and treatment of blue rubber bleb nevus syndrome in children

Zhao-Hui Deng, Chun-Di Xu, Shun-Nian Chen

Shanghai, China

Background: **Blue rubber bleb nevus syndrome (BRBNS) is characterized by distinctive vascular malformations of skin and the gastrointestinal tract, often leading to chronic anemia and intestinal bleeding. It usually presents right after birth or during early infancy. Though the disease is inherent, its occurrence is sporadic. Thus it is usually not timely diagnosed. We analyzed the clinical characteristics and treatment of this disorder in order to improve the diagnosis and treatment.**

Methods: **Three patients with BRBNS treated at our hospital during 2002-2003 and 39 patients from the literature reported during 1965-2003 were reviewed in terms of the diagnosis and treatment. BRBNS may be diagnosed as cutaneous cavernous hemangioma associated with the same lesion of the gastrointestinal tract and other organs.**

Results: **Our 3 patients suffered from cutaneous angioma and gastrointestinal hemangioma. In 39 patients reported in the literature, cutaneous angioma was observed in all of them, and gastrointestinal hemangioma in 31. Additionally, the lesions were also found in other organs such as the brain (7 patients), joint (2), liver (2), eye (1), kidney (1) and spleen (1). Cutaneous angioma was located on the surface of the skin, including body (93%), limbs (86%), hip (36%) and face (26%). Gastrointestinal hemangioma was more common in the small intestine (100%) than in the colon (74%) and stomach (26%). When the joint was involved by hemangioma, pathologic fracture or overgrowth of bone needed traction and amputation (1 patient respectively). For significant gastrointestinal bleeding, endoscopic techniques (8 patients), surgical excision (5), or both (1) were performed. Recurrent bleeding was successfully treated by endoscopic laser combined with steroid or interferon in one patient.**

Conclusions: **BRBNS in children presents atypical symptom and systemic complications. It should be dealt with seriously if gastrointestinal bleeding or orthopedic complication occurs. Treatment includes conservative, endoscopic and surgical options. Its recurrence with new angioma in the gastrointestinal tract needs laser-steroid therapy.**

World J Pediatr 2008;4(1):70-73

Key words: **blue rubber bleb nevus syndrome;**
diagnosis;
hemangioma;
therapy

Introduction

Blue rubber bleb nevus syndrome (BRBNS) is characterized by multiple cutaneous venous malformation in the skin, gastrointestinal tract, and less often in other organs, leading to chronic anemia and intestinal bleeding. BRBNS can occur at every stage from birth to adulthood. In children it presents with venous malformation in the skin and rarely with other complications. With the advancement of the disease, it may be complicated by gastrointestinal bleeding or orthopedic abnormalities. In this report we present 3 cases of BRBNS and a review of 39 cases from the literature reported from 1965 to 2003.[1-18] The report may heighten the awareness of physicians on this disorder because the early diagnosis is essential to the appropriate intervention.

Case report

Case 1

A 5-year-old boy was hospitalized because of anemia and melena. Physical examination revealed several cutaneous hemangiomas on the left foot, forearm, palm of hand and the second toe of the right foot. The black-blue, nodular and soft lesions varied from 0.5 cm to 3 cm in size. They were easily compressed and painful. Laboratory findings included hemoglobin level of 69 g/L,

Author Affiliations: Institute of the Shanghai Children's Medical Center, Jiao Tong University, Shanghai 200127, China (Deng ZH, Xu CD, Chen SN)

Corresponding Author: Zhao-Hui Deng, Institute of the Shanghai Children's Medical Center, Jiao Tong University, Shanghai 200127, China (Tel: 86-21-58732020; Email: dzhrj@163.com)

red blood cell (RBC) count 3.1×10^{12}/L, and platelet (PLT) 370×10^{9}/L. Gastrointestinal endoscopy and colonoscopy revealed 13 hemangiomas (0.5-3 cm in diameter) in the cardia, stomach, duodenal papilla, jejunum and sigmoid colon (Fig. 1). Biopsy of skin lesions showed cavernous hemangioma in the attenuated epidermis. There were thin vascular walls with typical endothelial cells and several fibrin thrombi. CT scan of the abdomen showed several masses in the liver and duodenal papilla. The boy was given transfusion of red blood cells and oral supplement of iron. Ten months later, however, he was readmitted for anemia and intestinal hemorrhage. Bleeding gastric lesions were resected with the help of endoscopy, and no anemia or signs of intestinal bleeding were observed in a 6-month follow-up period.

Case 2

A 6-year-old boy was admitted to the hospital because of recurrent dark stool in the past two years. He was born with cutaneous angiomas located at his right eye sockets and nose. The lesions became apparent with age. When he was 3 years old, gastroscopy showed several hemangiomas in the stomach, which were resected immediately. Histologically, the segments of the hemangiomas were found to be vascular malformations. After the operation, he developed melena. Physical examination revealed numerous bleb-like tumors on the bottom of the foot, the second toe of the right foot, the right eye socket and nose. The lesion varied in size from 0.5 cm to 2 cm. Gastrointestinal endoscopy revealed 7 maculopapular venous malformations in the duodenal bulb and the descending part of the ileum ranging from 1 cm to 3 cm in diameter.

His hemoglobin level was 43 g/L, RBC 2.1×10^{12}/L, and PLT 123×10^{9}/L. Cranial CT and chest X-ray showed nothing abnormal.

Blood transfusion or continuous iron therapy were prescribed instead of surgery or sclerotherapy.

Case 3

A 7-year-old boy was admitted to the hospital with complaints of recurrent dark stool and anemia for 2 years. He had cutaneous angiomas on his right neck from the age of 1 month. The lesions spreaded over the left lateral malleolus, and the second and third toe of the right foot (Fig. 2). At the age of 3 years, the lesions were resected, but recurred one year later. Microscopic features of the lesions were similar to those in case 1. Physical examination revealed numerous bleb-like tumors at the right neck, the left lateral malleolus, and the toe of right foot. Endoscopy showed 9 hemangiomas at the bottom of the stomach, ileum and colon. On admission, his hemoglobin level was 68 g/L, RBC 3.99×10^{12}/L, and PLT 155×10^{9}/L.

The boy was subjected to adult endoscopy and selective sclerotherapy.

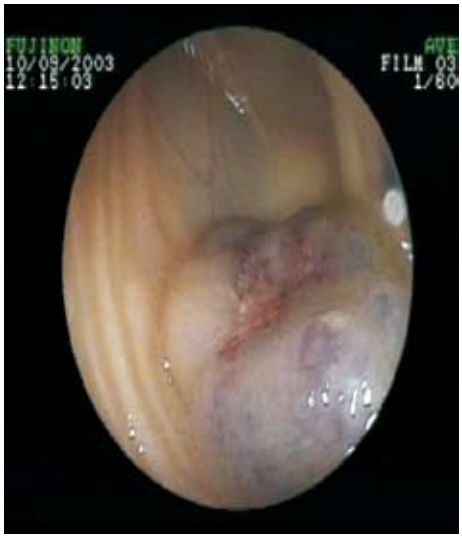

Fig. 1. Endoscopic view: hemangiomas in the jejunum.

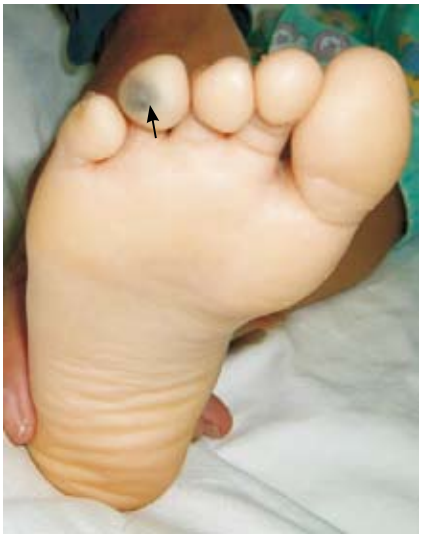

Fig. 2. Bluish-black lesion on the soles of the feet of the patient (arrow).

Table. Overview of the 39 cases of BRBNS reported from 1965 to 2003

Age of onset (*n*)			Sex (*n*)		Complications (*n*)							
Birth	Infancy	Childhood	Male	Female	Cutaneous	Gastrointestine	Liver	Slpeen	Eye	Urinary bladder	Joint	Brain
30	5	4	21	18	39	31	2	1	1	1	2	7

Discussion

BRBNS is a congenital disease characterized by multiple venous malformations in the skin and gastrointestinal tract. It is often misdiagnosed in the early stage because of its low incidence and atypical clinical symptoms. BRBNS presents with skin lesions at birth, but its diagnosis can only be confirmed in childhood or later when significant gastrointestinal bleeding occurs. Moreover, the small bowel is frequently involved and intestinal endoscopy is not widely used in children.[19,20]

In contrast to cutaneous lesion, gastrointestinal lesion tends to bleed easily, leading to massive hemorrhage and iron-deficiency anemia, which could be very severe and require blood transfusion. The 3 cases in our hospital presented with melena and anemia. Apart from gastrointestinal venous malformations, the other organs affected include the central nervous system, eye, liver, spleen, lung, urinary bladder and kidney. If a child has a cutaneous anginoma associated with another symptom either melena, epilepsy, hemoptysis, hematuria, paralysis or visual disorder, we should consider the possibility of BRBNS. Endoscopy, CT and MRI are the main tools for the diagnosis of the disease.[21-24] Histopathologically dilated vascular spaces are lined by a thin layer of endothelial cells and a thin or thick rim of fibrous tissue. BRBNS must be differentiated from the Rendu-Osler-Weber syndrome, Maffucci syndrome and Klippel-Trenaunay-Weber syndrome.[16-20,25]

Treatment of BRBNS is mainly symptomatic. Skin lesions are seldom treated unless they are cosmetically or functionally troublesome. In the reviewed cases, 2 had orthopedic abnormalities caused by therapeutic procedures, 1 was treated with traction because of a large hemangioma extending into the knee joint to cause fracture, 1 had the affected limb amputated because of functional impairment, 8 were treated by endoscopy because of severe gastrointestinal bleeding, 5 underwent surgical operation, 1 underwent surgery combined with endoscopic treatment, 2 with recurrent bleeding had laser and steroid or interferon therapy in combination.[26-31]

Treatment of gastrointestinal lesion depends on the extent of gut involvement and the severity of the condition. If there is no massive bleeding, conservative treatment is sufficient by blood transfusion and oral iron supplementation. INF as an inhibitor of vascular cell proliferation can also be effective in the treatment of vascular malformation.[32] In case of severe or recurrent hemorrhage, surgical wedge excision of angiomas or segmental resection of involved bowels is recommended.[27] Surgery combined with endoscopy or sclerotherapy has been proposed to shorten the time of operation and avoid unnecessary resection of certain part of the gut. Endoscopic coagulation with ND Yad laser is not effective to prevent recurrence of hemorrhage from lesions in the intestine as reported, but combination of laser and intermittent steroid therapy can successfully stop acute bleeding.[28-31] In our 3 patients, one gave up the treatment, one was successfully treated with endoscopy and followed up for 6 months without recurrence, and the other was prescribed for selective sclerotherapy.

In conclusion, we must keep in mind that melena or unexplained anemia and typical skin lesions may be the presentations of BRBNS, and gastrointestinal bleeding may be the chief complication of the disease. Recurrences of new angiomas in any part of the gastrointestinal tract are frequent, and close monitoring by upper and lower endoscopy is necessary.

Funding: None.
Ethical approval: Not needed.
Competing interest: No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article. .
Contributors: Deng ZH wrote the first draft of this paper. All authors contributed to the intellectual content and approved the final version. Xu CD is the guarantor.

References

1 Moodley M, Ramdial P. Blue rubber bleb nevus syndrome: case report and review of the literature. Pediatrics 1993;92:160-162.
2 Gonzalez D, Elizondo BJ, Haslag S, Buchanan G, Burdick JS, Guzzetta PC, et al. Chronic subcutaneous octreotide decreases gastrointestinal blood loss in blue rubber-bleb nevus syndrome. J Pediatr Gastroenterol Nutr 2001;33:183-188.
3 Oranje AP. Blue rubber bleb nevus syndrome. Pediatr Dermatol 1986;3:304-310.
4 Ertem D, Acar Y, Kotiloglu E, Yucelten D, Yucelten D, Pehlivanoglu E. Blue rubber bleb nevus syndrome. Pediatrics 2001;107:418-420.
5 Paller AS. Vascular disorders. Dermatol Clin 1987;5:239-250.
6 Hammond P, Lewindon P, Lewindon P. Gastrointestinal: blue rubber bleb nevus syndrome. J Gastroenterol Hepatol 1999;14:295-297.
7 Jain A, Kar P, Chander R, Khandpur S, Jain S, Prabhash K, et al. Blue rubber bleb nevus syndrome: a cause of gastrointestinal hemorrhage. Indian J Gastroenterol 1998;17: 153-154.
8 Kim SJ. Blue rubber bleb nevus syndrome with central nervous system involvement. Pediatr Neurol 2000;22:410-412.
9 Gallmann T, Boltshauser E. Blue rubber bleb nevus syndrome with CNS involvement. Klin Padiatr 1987;199:382-384.
10 Wong YC, Li YW, Chang MH. Gastrointestinal bleeding and paraparesis in blue rubber bleb nevus syndrome. Pediatr Radiol 1994;24:600-601.
11 Radke M, Waldschmidt J, Stolpe HJ, Mix M, Richter I. Blue

rubber-bleb-nevus syndrome with predominant urinary bladder hemangiomatosis. Eur J Pediatr Surg 1993;3:313-316.
12 Sumi Y, Taguchi N, Kaneda T. Blue rubber bleb nevus syndrome with oral hemangiomas. Oral Surg Oral Med Oral Pathol 1992;71:84-86.
13 Eirís-Puñal J, Picón-Cotos M, Viso-Lorenzo A, Castro-Gago M. Epileptic disorder as the first neurologic manifestation of blue rubber bleb nevus syndrome. J Child Neurol 2002;17:219-222.
14 Igawa T, Ooishi M, Ibe N, Ueno T, Takeda R, Yamada T, et al. A case of blue rubber bleb nevus syndrome with multiple hemangioma of the spleen and collateral circulation of the inferior mesenteric vein. Nippon Shokakibyo Gakkai Zasshi 1987;84:1331-1333.
15 Pan CH, Chen W, Chiang TP. Blue rubber bleb nevus syndrome and intussusception—a case report. Taiwan Yi Xue Hui Za Zhi 1984;83:1058-1063.
16 Ansari MN, Asharaf SN, Khan AA, Raza SM. Blue rubber bleb nevus syndrome. J Indian Med Assoc 1974;63:368-369.
17 Mccarthy JC, Goldberg MJ, Zimbler S. Orthopaedic dysfunction in the blue rubber-bleb nevus syndrome. J Bone Joint Surg Am 1982;64:280-283.
18 Fretzin DF, Potter B. Blue rubber bleb nevus. Arch Intern Med 1965;116:924-929.
19 Ng WT, Wong YT. Blue rubber bleb nevus syndrome: more lessons to be learnt. Eur J Pediatr Surg 2007;17:221-222.
20 Dobru D, Seuchea N, Dorin M, Careianu V. Blue rubber bleb nevus syndrome: case report and literature review. Rom J Gastroenterol 2004;13:237-240.
21 Kassarjian A, Fishman SJ, Fox VL, Burrows PE. Imaging characteristics of blue rubber bleb nevus syndrome. AJR Am J Roentgenol 2003;181:1041-1048.
22 Hales K, Connolly LP, Drubach LA, Mulliken JB, Fishman SJ. Tc-99m red blood cell imaging of blue rubber bleb nevus syndrome. Clin Nucl Med 2000;25:835-837.
23 Kawamoto K, Motooka M, Hirata N, Ueyama T, Kitagawa S, Shimoda Y, et al. Colonic submucosal tumors: a new classification based on radiologic characteristics. AJR Am J Roentgenol 1993;160:315-320.
24 D'Costa H, Hunter JD, O'Sullivan G, O'Keefe D, Jenkins JP, Hughes PM. Magnetic resonance imaging in macromelia and macrodactyly. Br J Radiol 1996;69:502-507.
25 Shepherd V, Godbolt A, Casey T. Maffucci's syndrome with extensive gastrointestinal involvement. Australas J Dermatol 2005;46:33-37.
26 Boente MD, Cordisco MR, Frontini MD, Asial RA. Blue rubber bleb nevus (Bean syndrome): evolution of four cases and clinical response to pharmacologic agents. Pediatr Dermatol 1999;16:222-227.
27 Czinner A, Leb J, Denes J. Successful surgical treatment of the "blue rubber bleb" nevus syndrome (viscerocutaneaous hemangiomatosis). Orv Hetil 1976;117:1889-1890.
28 Dòmini M, Aquino A, Fakhro A, Tursini S, Marino N, Di Matteo S, et al. Blue rubber bleb nevus syndrome and gastrointestinal haemorrhage: which treatment? Eur J Pediatr Surg 2002;12:129-133.
29 Ng WT, Kong CK. Argon plasma coagulation for blue rubber bleb nevus syndrome in a female infant. Eur J Pediatr Surg 2003;13:137-139.
30 Morris L, Lynch PM, Gleason WA, Schauder C, Pinkel D, Duvic M. Blue rubber bleb nevus syndrome: laser photocoagulation of colonic hemangiomas in a child with microcytic anemia. Pediatr Dermatol 1992;9:91-94.
31 Maunoury V, Turck D, Brunetaud JM, Marti R, Cortot A, Farriaux JP, et al. Blue rubber bleb nevus syndrome. 3 cases treated with a Nd:YAG laser and bipolar electrocoagulation. Gastroenterol Clin Biol 1990;14:593-595.
32 Apak H, Celkan T, Ozkan A, Yildiz I, Aydemir EH, Ozdil S, et al. Blue rubber bleb nevus syndrome associated with consumption coagulopathy: treatment with interferon. Dermatology 2004;208:345-348.

Received April 30, 2007
Accepted after revision November 20, 2007