

Blue Rubber Bleb Nevus Syndrome: associated with Severe GI Bleeding requiring one hundred Blood Transfusions

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Introduction

BRBNS is a rare entity characterized by distinctive venous malformation of skin and gastrointestinal tract, and less frequently of other sites.¹ The vascular lesions in the GIT bleed frequently leading to chronic iron deficiency anaemia. The lesions in other sites bleed rarely while skin lesions do not bleed at all.²⁻⁴

Gascoyen was the first person who, in 1860 noticed the association of cutaneous and GIT vascular lesions with severe GI blood loss.⁵ A century passed by and, in 1958, William Bennet Bean coined the term Blue Rubber Bleb Nevus Syndrome, a term quite nicely chosen to describe the typical blue, rubbery, bleb like vascular lesions.⁶ Medicine regards traditions, so it is also named as Bean Syndrome.

The syndrome affects both sexes and all races, mainly in White and Japanese races.^{7,8} Typically the venous malformations are present at birth or appear in early childhood but adult onset cases have been reported in the literature.^{1,9-11} The exact pathogenesis of the disorder is yet to be evaluated. Early diagnosis, detailed evaluation and a good follow up of these cases is recommended for effective management. We report here a case of BRBNS in an eight

years old girl who presented with typical cutaneous and vascular lesions with severe blood loss requiring about a hundred blood transfusions over a period of three years. To our knowledge this is the first case report of BRBNS from this country and also the first one of the reported cases associated with such severe bleeding and massive transfusion requirement and its associated complications.

Case Report

The patient is an eight years old girl, the product of a full term, uncomplicated pregnancy. At birth parents noticed two bluish macules over the anterior chest. With increasing age, similar new lesions appeared all over the body. These, lesions were soft, non-tender and of variable sizes. At three years of age, parents noticed an obvious change in the colour of her stools which turned tarry black.

The patient gradually became pale and developed symptoms of iron deficiency anemia. She was put on iron supplements and she showed clinical improvement. At the age of five years, iron supplements were discontinued without medical advice and within two months she became so pale that she needed a blood transfusion. Since then she is on regular blood transfusions with decreasing interval

between the two. During these three years, she continued to have black coloured stools. At the time of admission, she had received about one hundred blood transfusions. Her parents and five siblings were healthy and there was no family history of similar disorder.

Physical examination revealed an extremely pale child with a height of 117cm (5th centile), weight of 14kg (less than 5th centile). There were multiple bluish red vascular lesions over the face, trunk and upper and lower limbs. These were of variable sizes ranging from 2mm to 3cm. These lesions were soft, non-tender and could be emptied by firm steady pressure but refilled on releasing pressure. There was no involvement of mucous membranes. Rest of the physical examination was essentially normal.

Laboratory data showed a hemoglobin concentration of 3.5gm/dl, hematocrit of 12.6%, MCV of 85.7fL, MCH of 23.8pg and MCHC of 27.8gm/dl. ESR was 35mm/hr. Peripheral blood smear showed a mixed picture of hypochromic, microcytic and macrocytic red blood cells, with reticulocyte count of 0.5%. Bone marrow examination showed erythroid hyperplasia with mild megaloblastic changes. Coagulation studies and routine blood biochemistry was normal. Serologic studies for hepatitis B and C showed positive HCV antibodies. Stool examination at two different occasions was positive for occult blood. Barium meal and follow through failed to show any vascular malformation. Upper GI endoscopy and colonoscopy showed multiple characteristic bluish, bleb like lesions in the hypopharynx, distal esophagus, stomach, duodenum and in the rectum, sigmoid and descending colon. Majority of the lesions were solitary, one to two cm in diameter, with a shiny surface. Some of the lesions in the stomach and rectum were grouped together and appeared more fragile as compared to the solitary ones. Mild bleeding was observed from some of these lesions during endoscopy. RBCs labeled scan using 8.0mCi of Tc-99m pertechnetate tagged RBC'S failed to show any focus of abnormal radiotracer accumulation in the abdomen and pelvis except the usual sites of blood pool. Histopathology of skin lesions showed dilated vascular channels in the dermis lined by endothelial cells, supported by collagen fibers. Lamina contained simple red blood cells. These findings were consistent with the diagnosis of BRBNS.

During her three weeks stay in the hospital, patient needed three blood transfusions to keep her hemoglobin concentration above 10gm/dl. Because of the extent of GIT involvement, it was decided to manage her conservatively. Patient was given mega doses of iron, and folic acid. A three months follow up so far has shown promising results. The patient was discharged with a haemoglobin concentration of 10.9gm/dl and the two follow up visits, one month apart showed Hb of 10.2gm/dl and 8.0gm/dl respectively. ESR

also dropped from 35mm/hr to 10mm/hr. We are planning to sclerose the two larger lesions in the stomach and rectum in an attempt to minimize blood loss.

Discussion

Though there has been a good evidence of autosomal dominant inheritance in a number of reported pedigrees most of the cases of BRBNS are sporadic and it has been suggested that these cases arise as a result of new mutations.^{9,12-15} In one family only males appeared to be affected.¹⁶ Based on these reports, some cases of BRBNS have been registered as autosomal dominant in McKusick" catalogue of Mendelian inheritance in humans.¹² This has further been supported by Boon et al in an analysis of a locus of chromosome 9.¹⁷ Gallione et al have also identified a gene for familial venous malformation on chromosome 9.¹⁸ In our case, there was no history of similar lesions in the parents, her five sibs and other first degree relatives.

Cutaneous lesions are usually asymptomatic and do not bleed spontaneously. There is no evidence of malignant change in these lesions.^{13,19} Analogous lesions can occur in the gastrointestinal tract at all levels⁸ but they are most common in small intestine and distal colon^{3,14,20} and it is the second most commonly involved organ system in addition to skin. There appears to be no correlation between the number of skin and GIT lesions. In contrast to skin lesions, GIT lesions bleed frequently, causing iron deficiency which may require iron supplementation and blood transfusions.^{14,19,21-24}

The number of venous malformations in the GIT and severity of anaemia are correlated.²⁵ In our case, venous malformations were widespread and involved almost entire GIT, from hypopharynx to rectum. Constant oozing from these lesions resulted in severe blood loss requiring about a hundred blood transfusions over a period of three years. As a result patient became Hepatitis C antibodies positive.

The course of BRBNS is intriguing. New lesions may appear and existing ones may increase in size with time, and dormant lesions may become symptomatic. Chronic GI blood is the most important complication of BRBNS and a detailed evaluation of GIT is the most important part of the diagnostic work up. This also helps in choosing a suitable treatment strategy for the individual patient. Computed tomography, MRI, endoscopy, colonoscopy, barium studies, angiography and Tc-99m labelled RBC scan have all been used as diagnostic tools. Barium studies may fail to show the vascular lesions initially, as they may take time to grow large enough to become radiologically visible.¹³ When accessible to upper endoscopy and colonoscopy, these procedures have proven

more sensitive than barium studies and angiography.^{11,19,21,26-28} MRI may detect intra-abdominal lesions and maybe used for screening asymptomatic family members.^{28,29} In our patient, barium studies and Tc-99m labeled RBC scan were normal. Endoscopy and colonoscopy were most helpful in showing the vascular malformations.

Severe blood loss requiring transfusion therapy along with its potential complications is the most common complication of BRBNS. Other reported complications include intussusception, volvulus and infarction.^{30,31} Besides the cutaneous and GIT involvement, orthopaedic abnormalities are often associated with BRBNS.³² These include skeletal bowing, pathological fractures and bony overgrowth.³² They may also cause intraarticular bleed.³³ There is a reported case of BRBNS associated with gigantism of an arm requiring amputation.³⁴ In one case report blue naevi were associated with multiple enchondromes, as found in Maffucci's syndrome.³⁵ Our patient did not have any orthopedic involvement.

The venous malformations of BRBNS less commonly occur in a variety of other places, where they may provoke a wide spectrum of symptoms. These include liver, spleen, kidney, heart, lung, pericardium, pleura, peritoneum, oropharynx, nasopharynx, eyes, CNS, skeletal muscle, thyroid, parotid, bone, bladder, penis and vulva.^{4,6,7,13,19,26,28,29,32,36-42} There have been at least two reported cases of BRBNS complicating pregnancy.. In both cases, neonates had ventricular septal defects.^{43,44}

In addition to chronic iron deficiency anemia, other hematological abnormalities associated with BRBNS include thrombocytopenia³⁴ and chronic consumptive coagulopathy.³⁹

Differential diagnosis for BRBNS include multiple infantile hemangioma, Maffucci's syndrome, angiokeratoma corporis diffusum, hereditary haemorrhagic telangiectasia (Rendu-Osler-Weber syndrome) and Klippel Treauay-Weber syndrome.^{1,8,15,20}

Treatment for BRBNS largely comprises symptomatic treatment of iron deficiency anemia. A conservative approach is recommended whenever the bleeding episodes are mild.^{7,13} If vascular lesions are localized to one segment of GIT and are causing severe bleeding, resection of that segment should be considered.^{13,45,46} This approach should be cautiously used as recurrences are common after excision.¹³ GIT lesions can also be treated with endoscopic techniques such as sclerotherapy, band ligation and polypectomy.³³ Endoscopic laser (Nd:YAG) photocoagulation has also been successfully used.²⁹ When skin lesions are cosmetically unacceptable CO₂ laser coagulation can be considered as a

treatment option.²⁴ The role of pharmacological agents is less well described. Corticosteroids, interferon alpha and vincristine have all been used in some patients but lesions returned to their pretreatment level soon after the treatment was discontinued.^{46,47} In our patient, because of extensive involvement of GIT, surgery was not considered as a treatment option. The above mentioned pharmacological agents were not used in our patient because of their uncertain and controversial role.

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