CASE REPORT

Recurrent Severe Hypochromic Microcytic Anemia Multiple Blood Transfusions and Skin Lesions: Blue Rubber Bleb Nevus Syndrome

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Abstract:

Blue Rubber Bleb Nevus Syndrome (BRBNS) is a rare congenital disease of unknown etiology, presents with multiple venous malformations in skin and visceral organs particularly Gastrointestinal Tract (GIT). Skin lesions are asymptomatic, GIT bleb can bleeds. A 10-year female patient was presented with recurrent severe anemia that necessities several times hospital admission and blood transfusion. She was investigated for cause of anemia in every admission and investigations were repetition of same tests of previous admissions including invasive diagnostic procedure like bone marrow aspiration. Investigations have confirmed Iron Deficiency Anemia (IDA). She had small bluish-black compressible blebs in trunk and limbs since early age; the numbers of blebs are increasing with age. Endoscopy revealed small blebs in GIT. After blood transfusion and management of IDA, she has sent to gastrointestinal surgery department for specialized endoscopic management of GIT blebs. In this case the cause of IDA has defined chronic bleeding GIT blebs of BRBNS. We are reporting this rare disease to emphasize that skin blebs appeared from early childhood are typical of BRBNS that are indicator of vascular malformation of GIT as chronic bleeder in BRBNS. This understanding can contribute for right diagnosis at earlier point so several hospitalization, multiple transfusions, the cost of investigations could have been avoided. In addition, supportive management may be initiated early.

Keywords: Skin Nevi, Iron Deficiency Anemia, Blue Rubber Bleb Nevus Syndrome

Introduction:

Blue Rubber Bleb Nevus Syndrome (BRBNS) is a rare congenital disease characterized by multiple venous malformations in skin with or without visceral organs involvement. W B Bean [1] (1958) described Blue Rubber Bleb Nevus in skin and called Bean Syndrome.

The etiology of BRBNS is unknown. BRBNS are mostly sporadic (non-inherited) but an autosomal dominant variety found in familial cases connected to chromosome 9p [2]. Although it was mentioned no mutation had not found in vasculogenesis or angiogenesis [3], Soblet J *et al.* (2017) [4] postulated that somatic mutation at TEK (TIE2), gene encoding the endothelial cell tyrosine kinase receptor that is required for angiopoietins could be a cause for BRBNS.

The clinical presentation depends on which organ is affected. Skin blebs are the most common (93%) [5] and asymptomatic Gastrointestinal (GI) tract is second most common involved organ (76%) [5]. The GIT blebs mostly manifested as chronic bleeding and Iron deficiency anemia (IDA) [6, 7].

Management of BRBNS is conservative. Skin lesions are treated for cosmetic purpose. After supportive treatment of IDA, the management of GIT blebs depends on site and severity. GIT BRBNS is treated by antiangiogenetic medicine (steroids, interferon α-2a, sirolimus) to reduce bleeding. Endoscopical intervention or surgical

resection steps are taken in life-threatening situation or the potential bleeding source found [5].

Case Report:

A 10 year female patient was presented in the emergency department with severe pallor, dyspnea and just palpable spleen. She denied any obvious bleeding from any site such as hematemesis, hemoptysis, melena, hematochezia and epistaxis. Other negative history (h/o) is no nonsteroidal anti-inflammatory drugs ingestion, no liver disease, born of non-consanguineous marriage, no family history of bleeding disorder.

The past medical history was remarkable : she has been admitted approximately 12-14 times in different hospitals since age of six, the clinical scenario was same and treated by multiple packed red blood cells transfusions in every admission. Furthermore, High Pressure Liquid Chromatography (HPLC) and Bone Marrow Examination (BME) were done eight times and six times respectively. Every HPLC report was within normal limits, all BME were showed reactive bone marrow and no malignant infiltration.

Skin examination revealed multiple blue or bluish–black compressible verrucous well defined nevi on trunk and hand, axilla, foot, palm and buttock (Fig.1). Those are appeared in early childhood and one lesion in buttock just started to evolve. Histopathological examination of the lesion showed vascular malformation and hyperkeratosis of epidermis. There was no history of bleeding from skin lesions.

In addition a soft, moveable, 2.5×2.5 cm lesion was found over nape of the neck (Fig. 2) Clinical impression and Ultrasonography of the lesion was suggestive of lipoma. No oral mucosa lesion.

She had normal growth and development and no dysmorphism. On blood examination hemoglobin 4.2 gm%, MCV 67 fL, MCHC 24.5 g/dl, RBC morphology-hypochromic and microcytic, platelet count 18 5000/ mm^3, reticulocyte count 2.1 % , total leukocyte 6800 and RDW-CV 20.3% . Serum ferritin - 9.5 ng /ml.

Normal HPLC and Bone marrow examination already had done. Thyroid profile was within limit. Normal direct comb test negative. Prothrombin time and activated partial thromboplastin time were within normal limit. The screening of hepatitis B, hepatitis C viruses and HIV were negative. Antinuclear antibody test factor was non-reactive. Liver function test and renal functions were within normal limit. Upper GI endoscopy was done twice before attending our center, reported normal. Further upper GI endoscopy in our center revealed one small bluish lesion in stomach without any bleeding spot. We diagnosed a case of BBRNS and iron deficiency anemia. She was treated with packed cell transfusion and iron therapy. Patient was kept in

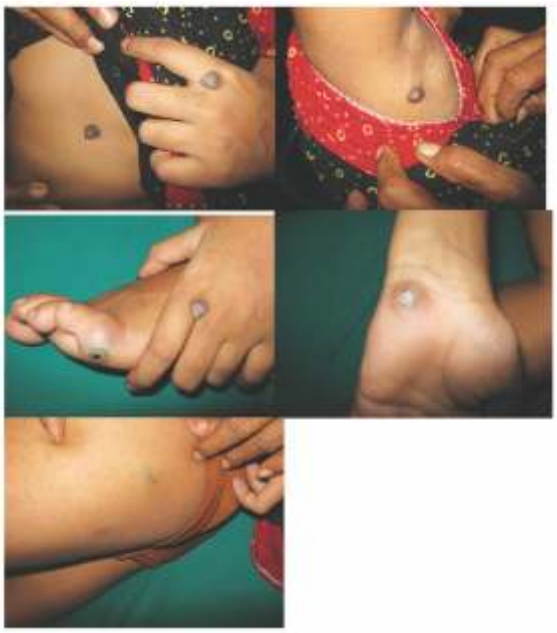

Fig. 1: Bluish-black Skin BRBNS on Trunk and Hand, Axilla, Foot, Palm, Evolving Lesion on Buttock

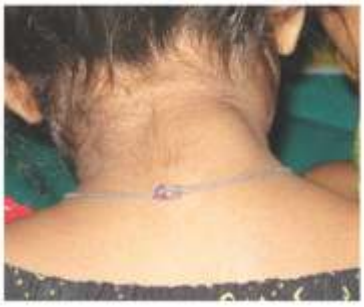

Fig. 2: Lipoma on neck

follow up at department of gastroenterology for further management.

Discussion:

After reviewing MEDLINE, Jin *et al*. [5] reported 200 BRBNS cases have been described so far in literature. Actual incidence of BRBNS may be much higher than published cases those are either not diagnosed or misdiagnosed and not recorded [8]. The majority BRBNS were reported from the United States and Japan [5]; Male: female ratio is 1:1. Rarely BRBNS have been from reported from India as an isolated case report [6, 7]. Clinical presentation is variable depending on organ involvement. Skin nevi are mostly asymptomatic and rarely painful [5]. Skin BRBNS start to evolution since birth or early childhood [9]. GIT BRBNS may present any site from mouth to anus [10]. The most common manifestation is chronic GIT blood loss and Iron Deficiency Anemia (IDA) [11]. Jin *et al*. [5] supported that all analyzed GI BRBNS in their review had chronic bleeding and IDA. Acute massive GIT bleeding is rare [11, 12].

The case-scenario of our BRBNS - several times emergency hospitalization for severe anemia, requiring multiple and massive transfusion - is uncommon. The similar presentation has been reported in only one case by Goraya *et al*. [6] and right diagnosis could not be done before.

The diagnosis of BRBNS stands on the characteristics skin lesions by clinical exam [13, 5, 8]. The skin lesions are characterized by 1-3cm sized bluish-black, rubbery, hyperkeratotic, verrucous, and compressible and easily refilled nevi. Histological, it is venous malformation filled with blood covered by a layer of endothelial cells [14]. The biopsy is not necessary for diagnosis [15].

This patient had a lipoma in nape of the neck. Vascular malformation like cystic lymphangioma in neck was reported with BRBNS, conjectured same embryological origin [16]. Benign adipose tissue tumor (lipoma) in BRBNS not reported yet , but adipose tissue overgrowth and vascular malformations, are reported in Clove syndrome [17] along with epidermal nevi. This patient had no brain anomaly like Clove syndrome.

GIT BRBNS are found any part of GIT but most common site small intestine. Capsule endoscopy or double balloon enteroscopy are the best investigations to find out small gut BRBNS [18]. So centers without such facilities can have missed the GIT BRBNS. A gastric lesion has seen in our case. The most important complication is chronic bleeding from GIT BRBNS. However, skin BRBNS and IDA are recognized as the most significant hallmarks of the disease [1, 11, 19, 20].

Of differential diagnosis: Osler-Weber-Rendu syndrome, Klippel-Trenaunay syndrome, and Maffucci syndrome are needed to be considered [5]. Our patient had no bleeding angioma or family history which is found in Osler-Weber-Rendu syndrome. Since she has no varicosities, bone deformities and chondrodysplasia then Klippel-Trenaunay syndrome and Maffucci syndrome are excluded respectively.

BRBNS is described in literature mostly as a case report. No standard guidelines regarding diagnosis or management are available. The

disease is misdiagnosed if clinician has not high suspicion [8]. The delay of correct diagnosis enhances morbidity like our case.

Treatment is challenging. Our management strategy was conservative – blood transfusion and iron therapy. The review literature revealed the mainstay of treatment [5] is supporting and continue lifelong, as high chance of recurrence after resection [12]. Vascular malformation tends to grow lifelong, do not have behavior [21] like hemangiomas that cease to grow with the advancement of age. Endoscopic or surgical intervention advocated in massive hemorrhage or other complication [11, 12]. Mortality is rare due to GIT bleeding in BRBNS. In review, one BRBNS has died due to GIT bleeding [5].

Learning points

1. Diagnosis of BRBNS based on clinical examination of skin, the characteristics lesions.
2. Iron deficiency anemia and skin BRBNS the significant hallmark of the disease. Small gut lesions may be difficult to identify as all center is not equipped with pediatric capsule endoscopy
3. Blood transfusion and iron therapy mainstay of therapy.
4. Surgical or endoscopic intervention better to avoid as high chance of recurrence

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