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Case Report

A rare case of blue rubber bleb nevus syndrome

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ABSTRACT

Blue rubber nevus bleb syndrome is a rare disease characterized by venous malformations and hemangiomas of skin and visceral organs. The incidence is very low, approximately 200 cases reported till date. Clinical manifestations can be present since birth or start in early childhood or adolescence. Most common symptom is gastrointestinal bleeds and secondary iron deficiency anemia. A 16-year-old female child presented with complaints of easy fatigability and breathlessness since 2 months, hematemesis and melena since 2 days. At admission, child was hemodynamically stable, Head to toe examination revealed severe pallor, angiokeratomas in oral cavity and multiple lesions over extremities and abdomen. Lab investigations revealed pancytopenia. Capsule endoscopy done revealed multiple lesions throughout stomach and entire small bowel measuring 0.5×0.5cms. Hence, considering as blue rubber bleb nevus syndrome received blood transfusion and started on sirolimus. Currently child is asymptomatic and continued with oral Sirolimus. Blue rubber bleb nevus syndrome is also known as Bean syndrome. It is a rare syndrome of venous malformations that arise in the skin and gastrointestinal tract. Usually involves cutaneous (93%), gastrointestinal (76%), central nervous system (13%), liver (11%), and muscles (7%). The small bowel is the most common site of gastrointestinal tract involvement; however, lesions can occur anywhere from the mouth to the anus. Treatment involves correction of anemia with transfusions and iron supplements. Pharmaceutical agents such as propranolol, octreotide, interferon alpha, thalidomide, antibrinolytics and most recently sirolimus have also been utilized. Blue rubber nevus bleb syndrome should be considered in any children with history of anemia, hematemesis and melena with cutaneous vascular malformations.

Keywords: Blue rubber bleb nevus syndrome, Vascular malformations, Capsule endoscopy

INTRODUCTION

Blue rubber bleb nevus syndrome also known as Bean syndrome, is a rare syndrome of venous malformations that arise in the skin and various organ systems1. Patients present with multiple venous malformations in the liver, spleen, heart, eye, and central nervous system. BRBNS was first described in 1860 by Gascoyne and later described in 1958 by William Benett Bean2.It is usually a sporadic disorder; however, autosomal dominant modes of inheritance are reported1. Approximately 200 cases have been reported in the literature. It has been identified in all races, with Whites most frequently affected1.Here we report a case of BRBNS with severe anemia secondary to gastrointestinal blood loss with venous malformations in multiple organs.

CASE REPORT

A 16-year-old female child second born to non-consanguineous married couple with normal birth and developmental history, immunized till date presented with complaints of easy fatigability since 2 months, fever 10 days, hematemesis and melena since 2 days.

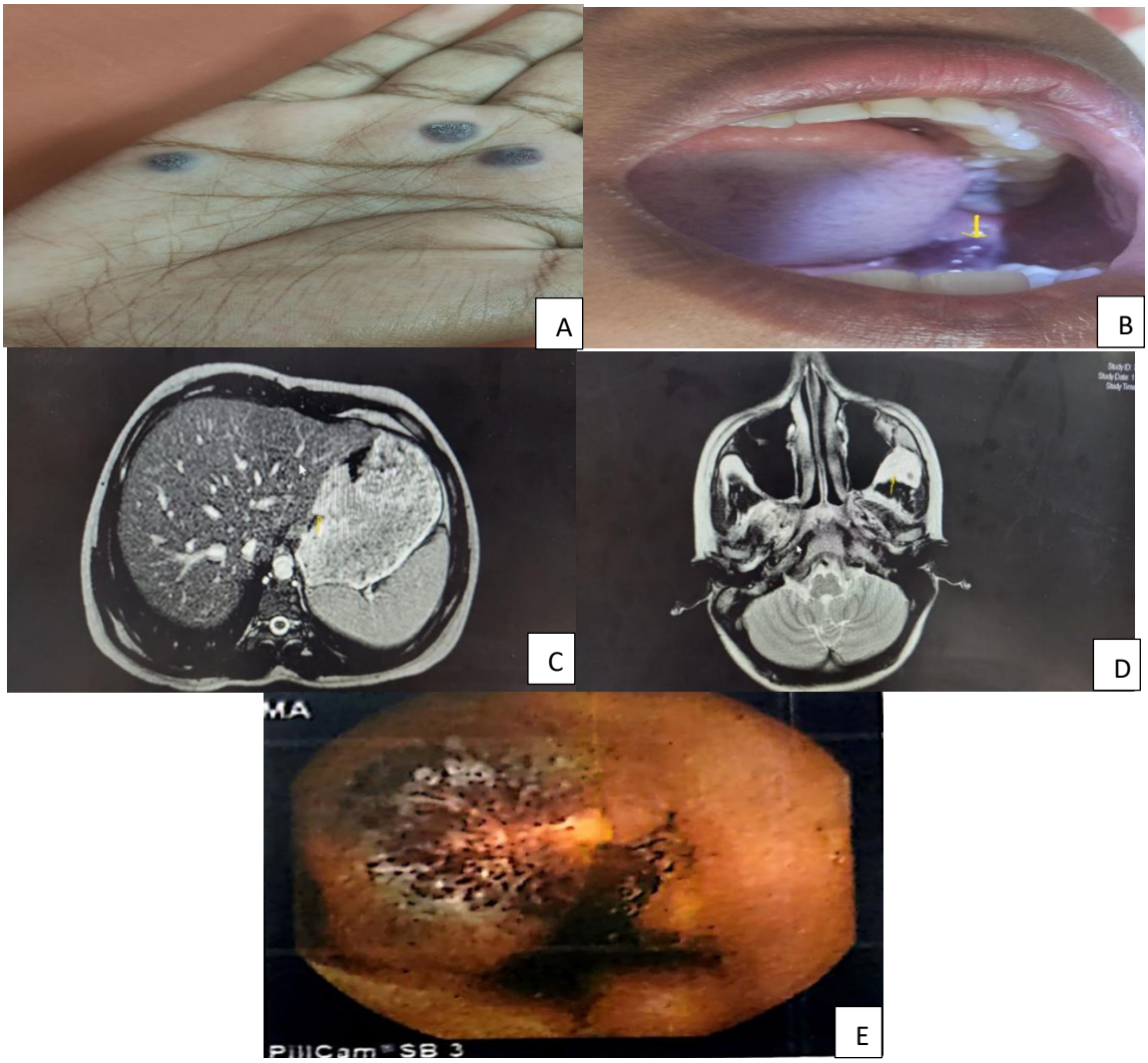

Figure 1: A) Bluish, rubbery, non-tender, compressible lesions on the palmar surface of hands. B) Mucocutaneous lesions in oral cavity. (C&D) T2/SPAIR images of brain and abdomen showing multiple hyperintense ill-defined areas, blooms on GRE, bright on DWI ND ADC with persistent delayed enhancement suggestive of slow flow vascular malformations-consistent with blue rubber bleb syndrome. E) Capsule endoscopy showing vascular malformation in the esophagus.

Child was hemodynamically stable, underweight (BMI - 13.8). Head to toe examination revealed pallor, rubbery, bluish, non-tender, compressible lesions measuring 0.5×0.5 cm lesion in oral cavity and multiple similar lesions over extremities and abdomen. Systemic examination was unremarkable. Initial evaluation done revealed Hb 3.5 g/dl, total counts 2600 cells/mm^3, platelets -91000/mm^3, MCV-78fl, MCH- 25.3 pg, MCHC- 32.3 g/dl, PCV-30%, Total Iron-14mcg/dl, TIBC-313 mg/dl, transferrin saturation 4.2%, PS - microcytic hypochromic anemia with leucopenia and thrombocytopenia. Stool routine showed plenty of Rbcs. RFT and LFT were normal. USG abdomen was normal. Gastro duodenoscopy revealed bluish lesions 0.5 cm to 1 cm in fundus and body of stomach, colonoscopy revealed similar lesion in recto sigmoid region. Capsule endoscopy done showed multiple bluish raised lesions throughout stomach and entire small bowel measuring 0.5×1 cm. Skin biopsy done revealed sub epidermal cystically dilated vascular spaces lined by flattened epithelium (hemangiomas). Child received pRbc transfusions and post transfusion Hb improved to 9.7 g/dl. MRI T2/SPAIR images of brain and abdomen showed multiple hyper intense ill-defined areas, blooms on GRE, bright on DWI ND ADC with persistent delayed enhancement suggestive of slow flow vascular malformation.

DISCUSSION

The maximum number of patients with BRBNS were associated with mutations in TEK (TIE2), that encodes TEK receptor tyrosine kinase.[3] BRBNS is caused by double (cis) mutations in the TEK gene.[1] This transmembrane receptor is part of angiogenesis, including destabilization of existing vessels, endothelial cell migration, tube formation, and stabilization of newly formed tubes by mesenchymal cells.[1] This TEK receptor

when activated, releases chemical signals that facilitates communication between endothelial cells and smooth muscle cells. This leads to new blood vessel formation and safeguards the structure and integrity of these blood vessels.[1] The TEK receptor is constitutively active in blue rubber bleb nevus syndrome due to somatic activating mutations.[1] This leads to unregulated angiogenesis1.Histopathological evaluation of lesions reveals blood filled ectatic vessels lined by a single layer of endothelial cells which is surrounded by a thin layer of connective tissue. Some cases dystrophic calcification may be present.[1] Patients with blue rubber bleb syndrome may present at birth or in earlier in life with multiple blue to violaceous soft compressible nodules on the skin or mucous membranes.[3] The typical skin lesions are described as rubbery in consistency and may be tender to palpate.[4] These lesions are variable in size ranging as small in size from a few millimeters to up to 4 to 5 cm in diameter.[1] Venous malformations can involve any system including the heart, spleen, liver, central nervous system, and gastrointestinal tract. The small bowel being the most common site of gastrointestinal tract involvement. Venous malformations being slow-flow lesions, are prone to thrombosis.[1] The most common symptoms in the gastrointestinal (GI) tract are hemetemesis and melena leading to IDA, and may also present with severe complications such as rupture, intestinal torsion, and intussusceptions, gangrene, volvulus and infarction.[2] The vascular malformations that appear in BRBNS are variable and can include telangiectasia, capillary hemangioma, cavernous hemangioma, venous angioma and on rare occasion arteriovenous fistula.[2] The types of vascular lesions that can be seen are as follows - I) large, venous malformations that obstruct vital tissues. II), thin-walled sac filled blood, easily compressible and slowly refilling when pressure is released. This is the most common type. These can be asymptomatic or can be painful or may be associated with hyperhidrosis. III) these lesions are blue-blackish irregular macula or papule which rarely pales under pressure.[2] Our patient had Type II lesion.GI tract lesions can be diagnosed with the help of Barium swallow, upper and lower Endoscopy, nuclear imaging, abdominal CT scan and MRI.BRBNS must be differentiated from hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome), Klippel-Trenaunay syndrome, and Maffucci syndrome.[2] All of these diseases are characterized by different forms of vascular malformations. Osler-Weber-Rendu syndrome is characterized by hemorrhagic pinpoint angiomas, recurrent epistaxis, telangiectasia and a positive family history.[2] Maffucci syndrome presents with diffuse vascular malformations in the skin and soft tissues, bone malformations, and chondrodysplasia.[2] Klippel-Trenaunay-Weber syndrome is characterized by varicosities, hypertrophy, and deformities of soft tissues and bones.[2] Cutaneous lesions can be treated by various modalities like electrodessication and curettage, liquid nitrogen, carbon dioxide laser or surgery. Bleeding from GI lesions is managed with, endoscopic coagulation, endoscopic sclerotherapy and endoscopic laser photocoagulation.[1] Pharmaceutical agents such as propranolol, octreotide, corticosteroids, interferon alpha, thalidomide, antifibrinolytics, and most recently sirolimus have also been utilized.[3] These have been used based on extrapolation of their efficacy in infantile hemangiomas and other vascular anomalies.[3] Sirolimus has emerged as a new medical treatment option for both vascular tumors and vascular malformations. It is as a mammalian target of rapamycin (mTOR), capable of integrating signals from the PI3K/AKT pathway to coordinate proper cell growth and proliferation. Therefore, sirolimus has emerged as a specific option for “proliferative” vascular tumors through the control of tissue overgrowth disorders caused by inappropriate activation of the PI3K/AKT/mTOR pathway as an antiproliferative agent.[8] It is a mammalian target of rapamycin (mTOR) kinase inhibitor] that reduces the sensitivity of T cells and B cells to interleukin-2 (IL-2), inhibiting their activity.[7] Our patient was started on oral sirolimus 1mg twice a day (0.06 mg/kg/day) and followed up. The child currently on Sirolimus and has no further hemetemesis or melena and no increase in size of mucosal or skin lesions. The child has not required further blood transfusions.

Cerebral cavernous malformations (CCMs) are abnormally large collections of "low flow" vascular channels without brain parenchyma intervening between the sinusoidal vessels.[5]

CCMs are the second most common vascular finding on MRI. Sluggish blood flow through dysplastic channels results in recurrent thrombosis, calcification, and deposition of hemosiderin along the margins of the lesion5. Intracranial bleeds can result in focal neurologic deficits (FND), seizure, or a headache prompting the patient to present for evaluation. The most common clinical manifestations are seizures (50%), intracranial hemorrhage (25%), and focal neurological deficits (FND) without radiographic evidence of recent hemorrhage (25%).[5]

CONCLUSION

BRBN can be considered in any children presenting with gastrointestinal bleeding, anemia and vascular malformations, as prompt treatment significantly reduces morbidity and need for surgical intervention.

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