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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

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ABSTRACT

Blue rubber bleb nevus syndrome (BRBNS) is a rare disorder comprised of venous malformation mostly involving the skin and gastrointestinal (GI) tract but can also involve other visceral organs. The most predominant site of GI tract involvement is the small bowel. In patients with GI lesions, treatment depends on the severity of bleeding, and extent of involvement. Conservative therapy with iron supplementation and blood transfusion is appropriate in cases with mild bleeding but in severe cases endoscopic and surgical interventions would be beneficial. Also, medical therapy with sirolimus significantly reduces bleeding. A 20-year-old woman was referred to our hospital after transfusion of six units of packed cell because of several episodes of lower GI bleeding within the past three months in the form of melena and a single episode of hematochezia. Her last hemoglobin level before admission was 10mg/dl. She underwent various unsuccessful investigations since she was eight years old to find the origin of refractory iron deficiency anemia. In upper endoscopy, five bleeding polypoid lesions were discovered in the jejunum. Lesions were excised by snare polypectomy. Over a six-month follow-up period, no signs of lower GI bleeding were noted and the patient had a normal hemoglobin level.

KEYWORDS:
Blue rubber bleb nevus syndrome, Double balloon enteroscopy, Submucosal dissection, Endoscopy, Anemia, Small bowel

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INTRODUCTION

Blue rubber bleb nevus syndrome (BRBNS) is an uncommon disorder comprised of multiple venous malformations mostly in the skin and gastrointestinal (GI) system but can also involve other organs such as the muscles, lung, eye, kidney, joints, and nervous system.[1-3] Cutaneous lesions have various appearance ranging from a blue-purple papule to a large vascular tumor.[4] Intestinal lesions can cause abdominal pain, intussusception, volvulus, infarction and GI bleeding.[4] BRBNS is more prevalent in childhood and adolescence but also lesions can be observed at birth.[5,6] Occurrence is mostly sporadic but autosomal dominant inheritance has been suggested previously.[7]

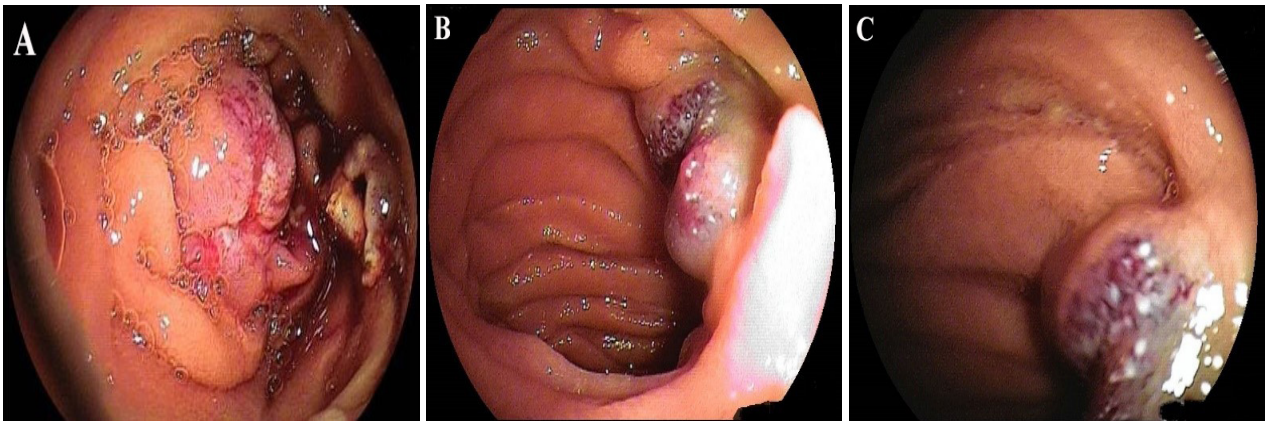

Fig.1: Venous malformations located in jejunum observed during double balloon enteroscopy

Lower GI bleeding is a common manifestation of this syndrome ranging from an obscure lower GI bleeding to a massive life threatening bleeding.[8] Treatment options depend on the extent of and severity of involvement and bleeding. Conservative treatments can be a method of choice in mild bleeding but in severe forms, surgical and endoscopic interventions are necessary.[5,9,10] Double balloon enteroscopy has an important diagnostic-therapeutic role in small intestine pathologies. This method can be used to observe and excise BRBNS intestinal lesions.[11] We reported a 20-year-old woman with BRBNS manifested with obscure GI bleeding. Double balloon enteroscopy was used for diagnosis and finally the lesion was excised by snare polypectomy.

CASE REPORT

A 20-year-old woman was referred to our hospital after transfusion of six units of packed cell because of several episodes of lower GI bleeding from three months ago in form of melena and a single episode of hematochezia. Her last hemoglobin level before admission was 10 mg/dl. She underwent various unsuccessful investigations since she was eight years of age to find the origin of refractory iron deficiency anemia. Previously, she did not have a history of GI bleeding (melena and hematochezia), nausea or vomiting, diarrhea or constipation, abdominal pain, fever, significant weight loss, NSAIDs usage, or any comorbidities. In physical exam the patient was pale. No skin lesion was revealed. In our medical center upper and lower endoscopy did not shown any pathologies. Thus, we decided to perform an oral double balloon enteroscopy. Sedation initiated with pethidine 50 mg and diazepam 10 mg and was then adjusted according to the patient's demand. Vital signs were normal and stable during the procedure. Five bleeding polypoid vascular lesions were discovered in the jejunum (figure 1). The size of the largest lesion was 15×15 mm. After injecting epinephrine in lesions to bulge them, all of them were resected by snare and referred to a pathologist. Histopathology reported multiple hemangiomas. Two weeks later, the patient underwent oral double balloon enteroscopy again with the same sedation protocol. No signs of bleeding were found and hemoglobin level rose. After six months of follow-up, no signs of lower GI bleeding were noted and the patient had a normal hemoglobin level.

DISCUSSION

BRBNS is a rare syndrome presented with venous malformations mostly involving the skin and GI tract but can affect other organs such as the muscles, joints, eye, lung, kidney and nervous system.[3] Pathophysiology of the disease is not fully understood and is still unclear. Most of the cases are sporadic but autosomal dominant inheritance has been suggested previously.[7] It has been reported that stem cell factor/c-kit signaling system may cause vascular overgrowth.[12] Stimulation of mammalian target of rapamycin complex (mTOR) and mutations in TEK gene can also lead to angiogenesis in patients with

BRBNS.[13,14] Our patient did not undergo genetic analysis because of poor socioeconomical level. BRBNS, Maffucci syndrome, Osler–Weber–Rendu syndrome and Klippel–Trenaunay–Weber syndrome are differential diagnoses of skin and GI hemangiomatosis and accurate diagnosis is important.[15,16] Cutaneous lesions have three types: soft easy compressing bluish papules which quickly refill after compression, large vascular masses that can affect adjacent structures, and macular bluish lesions with irregular border. These lesions are not usually painful or bleed spontaneously. Lesions can be observed at birth but mostly present in childhood and adolescence. Excision or laser ablation is the method of choice in cutaneous lesions.[3,17] GI lesions can be observed in all parts of the GI tract from the mouth to anus. Lesions range from 1 to 10 cm. The small intestine is the most commonly involved site. Various GI presentations can be seen. Patients may have upper or lower GI bleeding for a long period of time. Lower GI bleeding is the most common symptom ranging from obscure to massive bleeding leading to anemia.[3,18] Some other rare complications may occur such as perforation, intussusception, intestinal torsion and infarction,[16,19] or hematological complications such as Disseminated intravascular coagulation and thrombocytopenia.[3,6,20] Mortality in patients with BRBNS was mostly reported in severe GI involvement such as intussusception, perforation and volvulus.[21-23]

Barium swallow, upper and lower Endoscopy, nuclear imaging, abdominal CT scan and MRI can be beneficial in diagnosis of GI tract lesions. Barium swallow can elucidate polypoid lesions in the upper GI tract but cannot differentiate vascular malformations from other types of lesions. Colonoscopy is an accurate method in discovering colonic lesions as well as video capsule endoscopy and double balloon enteroscopy that could be used as an ideal diagnostic measure for small intestine evaluation. The former is a non-invasive method that can record a video whole intestine specially, small intestine and the latter is an invasive method for evaluation of small intestine pathologies. MRI is beneficial in finding lesions located in organs such as spleen and liver. Scintigraphy is another non-invasive diagnostic method to find the source of GI bleeding when endoscopic procedures are unable to find the source of bleeding. Aggregation of radio nucleotide in venous malformations can reveal the GI lesions.[18,24]

Treatment of GI lesions depend on the extent and severity of involvement. In mild bleedings, iron supplementation therapy and appropriate diet can compensate Iron Deficiency Anemia (IDA). In some occasions blood transfusion is necessary.[5] Pharmacological treatment by corticosteroids, INFα and β-blockers have been tried before but did not significantly affect bleeding.[25] On the other hand, chronic subcutaneous octreotide has been reported to be effective in decreasing patients' demand for blood transfusions.[26] Recently, low dose sirolimus is beneficial in reducing GI bleeding in patients with BRBNS and can be an alternative to blood transfusions. Sirolimus inhibits mTOR complex which is associated with angiogenesis. Thus, it can decrease the size of GI venous malformations.[27,28] Before performing an invasive surgical operation, precise evaluation of the number of lesions and extent of involvement is necessary. Surgical excision such as partial gastrectomy, partial small bowel resection is preferred in focal GI involvement, although in cases with widespread GI involvement is not the method of choice. Moreover, in some complications including torsion, intussusception or perforation, surgical intervention is necessary.[25] Extensive resection increases the risk of short gut syndrome in these patients.[21] In patients with multi-organ involvement, medical therapy with sirolimus should be considered.[29] Endoscopic treatments are another invasive method of excising GI lesions by means of sclerotherapy, laser photocoagulation, band ligation, Argon plasma coagulation (APC), snare mucosectomy and endoscopic submucosal dissection.[30] Several studies suggested to avoid endoscopic procedures such as APC in the small intestine because of its thin wall and risk of perforation, while other authors reported that endoscopic procedures such as polypectomy and band ligation increased the risk of perforation and ulceration in transmural lesions.[31,32] Therefore, surgical full thickness wedge resection seems to be a better option.[33] We reviewed English articles containing endoscopic treatments in cases with BRBNS reported in last 5 years in table 1.

CONCLUSION

Accoring to the results of our review and also our case presentation, in the case of patient with prolonged Iron Deficiency Anemia, Blue Rubber Bleb Nevus Syndrome can be considered as differential diagnosis, however BRBNS is a rare disease and also Double balloon enterscopy

Table 1: Review of Endoscopic Treatments in Cases with BRBNS

Patient number	Reference	Sex	Age at diagnosis	Site of involvement	Treatments	Type of endoscopy treatment	Follow-up results
1	21	M	4	Skin-GI-Angioker-atoma of left tight	Endoscopic	APC- Band ligation-Sclerosing agent	Blood transfu-sions requirement decreased
2	21	F	15	GI	Endoscopic	APC	Blood transfu-sions requirement decreased
3	21	M	1	Skin-GI-Muscle	Endoscopic-Surgery	APC	Asymptomatic
4	21	M	5	Skin-GI	Endoscopic-Surgery	APC	Stable
5	21	M	12	Skin-GI	Endoscopic-Surgery	Intra-operative enteroscopy with snare mucosectomy- APC	Anemia- Iron infusion dependent
6	21	M	1	GI- CNS- Eyes	Endoscopic-Sirolimus	APC	Asymptomatic
7	21	F	2	GI- Skin- Joints-Angiokeratoma of second left toe and right thigh	Endoscopic-Surgery-Sirolimus	APC	Scarce response to endoscopic and surgical treatment
8	21	F	7	GI- Skin- Joints-Parotid Glands- Left kidney	Endoscopic-Surgery-Thalido-mide- Inter-feron alpha-2a-Predniso-lone-Propanolol-Octreotide	Intraoperative enter-oscopy with surgical wedge excision of small bowel lesions	Still blood transfusion dependent- Inter-feron alpha-2a side effects
9	21	F	5	Skin- GI- CNS-Spine- Muscles-Joints	Endoscopic-surgery- Tha-lidomide-Tranexamic acid- Siroli-mus	Sclerosing agent- In-traoperative enteroscopy with surgical wedge excision of small bowel	Active Intussusceptions-Thalidomide side Effects- Good response to siroli-mus, relapse when the drug was stopped, required surgery- Occa-sional blood per rectum, no blood transfusion re-quirement
10	21	M	1	Skin- GI- Lungs	Endoscopic-Surgery-Prednisolone	Sclerosing agent	Blood transfusions requirement decreased
11	34	M	21	Skin- liver- GI	Endoscopy-Surgery-Octreotide-Sirolimus	Sclerosing agent-APC- ligature with envelope	Maintains an excellent con-trol of anemia and gastrointestinal bleeding
12	35	F	13	GI	Endoscopy-Surgery	Sclerosing agent	Failure of endo-scopic manage-ment and bleeding recurred, surgery was planned

Patient number	Reference	Sex	Age at diagnosis	Site of involvement	Treatments	Type of endoscopy treatment	Follow-up results
13	17	F	19	Skin- GI- Pleura- Liver- Spleen- Ovary	Endoscopy- Surgery- Beta blocker	Band ligation- APC- intra operative endoscopy	No bleeding and anemia for 5 years after endoscopy and surgery
14	36	M	19	Skin- GI	Endoscopy- Surgery- Sirolimus	Sclerosing agent- APC	Anemia resolved and patient's weight increased
15	37	M	9	Skin- GI	Endoscopy	Sclerosing agent- APC	Asymptomatic
16	30	F	18	GI	Endoscopy	Endoscopic submucosal dissection	No bleeding happened
17	38	F	10	Skin- GI- Cerebellum- Iris	Endoscopy	Sclerosing agent	She did not manifest anemia
18	39	M	13	Skin- GI	Endoscopy	Sclerosing agent	No further blood transfusion was needed
19	40	M	21	GI	Endoscopy	Endloop-snare	No bleeding of perforation during 6 months of follow up
20	41	F	19	Skin- GI	Endoscopy	Snare mucosectomy	No recurrence of the hemangiomas in the patient's stomach 6 months after endoscopic treatment
21	42	F	24	Skin- GI	Endoscopy	Sclerosing agent	The patient had no obvious drop in hemoglobin during the process
22	43	F	21	GI	Endoscopy	En-bloc endoscopic mucosal resection (EMR) using a symmetric snare- APC	There was no bleeding recurrence in two years of follow-up
23	44	F	34	GI	Endoscopy- surgery	Intra operative endoscopy with band ligation	Good clinical condition and did not need further blood transfusions.
24	45	F	15	Skin- GI	Endoscopy- surgery	Intra operative endoscopic band ligation	After 6 months she had no discomfort

can play crucial role in the diagnosis and treatment of these patients.

ETHICAL APPROVAL

There is nothing to be declared.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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