A 10-year delayed diagnosis of blue rubber bleb nevus syndrome characterized by refractory iron-deficiency anemia: A case report and literature review

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Abstract

Rationale: Blue rubber bleb nevus syndrome (BRBNS) is a rare vascular disorder consisting of multifocal venous malformations. Delayed diagnosis or misdiagnosis frequently occurs in patients without typical cutaneous lesions or gastrointestinal bleeding symptoms. This article reports a 10-year case of delayed diagnosis of BRBNS detected by capsule endoscopy.

Patient concerns and diagnosis: A 15-year-old girl presented with refractory iron-deficiency anemia (IDA) for 10 years, without any hemorrhagic signs or noticeable cutaneous lesions, which led to her obvious physical growth retardation. Capsule endoscopic examination revealed dozens of vascular blebs distributed from the jejunum to the ileum and a site of active bleeding. Hence, she was diagnosed with BRBNS.

Interventions: Laparotomy was performed with resection of the small bowel lesions, and iron supplementation was prescribed for 3 months. Postoperatively, the patient had an uncomplicated course.

Outcomes: On follow-up after 3 years, IDA in this patient was cured and she did not require further blood transfusion and showed excellent vigor.

Lessons: A high index of suspicion for BRBNS and adequate endoscopy examination will help to identify the origin of refractory IDA in older children, particularly in patients with vascular lesions of the skin.

Abbreviations: BRBNS = blue rubber bleb nevus syndrome, CT = computed tomography, FOBT = fecal occult blood test, GI = gastrointestinal, IDA = iron-deficiency anemia.

Keywords: blue rubber bleb nevus syndrome, diagnosis, refractory iron-deficiency anemia

1. Introduction

Blue rubber bleb nevus syndrome (BRBNS) is an uncommon disorder with characteristic venous malformations of the skin and visceral organs, predominantly in the gastrointestinal (GI) tract. An almost ubiquitous hallmark of this syndrome is several to hundreds of blue-purple cutaneous lesions. Patients may have secondary chronic anemia due to GI bleeding, which may be difficult to detect. Early diagnosis and appropriate treatment can significantly improve quality of life and avoid fatal complications. Here, we present a 15-year-old girl who had refractory iron-deficiency anemia (IDA) for 10 years without typical skin lesions of BRBNS or hemorrhagic symptoms. After capsule endoscopy, we finally cured her IDA with laparotomy and resection of GI lesions.

2. Case report

A 15-year-old girl presented to our outpatient department with refractory IDA that required multiple blood transfusions and iron supplementation for survival over the past 10 years. She was born with 2 pea-sized cutaneous nodules on her right opisthenar, which were increased in size over time and were resected at a local hospital with a diagnosis of angioma when she was 6 months old. Ten years ago, she experienced pallor and fatigue and was evaluated at numerous hospitals but was only treated with blood transfusions without identifying the underlying etiology of refractory IDA. Her parents and brother (10 years old) had no similar skin lesions or anemia. Recently, the symptoms were aggravated, resulting in the need for increased blood transfusions; the patient visited our hospital for further diagnosis and treatment. She denied hematochezia, melena, abdominal pain, hematemesis, hemoptysis, menorrhagia, recurrent gum bleeding, or epistaxis. On physical examination, mild pallor was noted.
Her vital signs were normal but she showed obvious physical growth retardation, with a height of 140 cm and weight of 30 kg. Cutaneous examination showed a bluish nodule on the right chest wall (Fig. 1A). The findings on physical examination were unremarkable.

A series of routine blood analyses showed severe anemia characterized by small hypopigmented red blood cells. The lowest hemoglobin level was 20 g/dL (mean corpuscular volume 58.5 fl, mean corpuscular hemoglobin 16.2 pg, and mean corpuscular hemoglobin concentration 280 g/dL). White blood cell and platelet counts were normal. Serum ferritin level was <1 ng/mL, serum iron was 2.3 μmol/L, and total iron binding capacity was 74.6 μmol/L. The levels of serum folic acid and vitamin B12 were normal. Coomb’s test, erythrocyte osmotic fragility test, and hemoglobin electrophoresis also showed normal results. Liver function, kidney function, and blood clotting function were normal. Bone marrow aspiration revealed erythroblasts with marked hyperplasia and depleted bone marrow iron stores. Repeated fecal occult blood test (FOBT) and routine urine testing showed negative results. Contrast-enhanced computed tomography (CT) of the chest and abdomen showed no positive findings. Gastroscopy demonstrated antral gastritis, gastric and duodenal mucosal erosions, and a mass in the descending part of the duodenum (Fig. 2A). Colonoscopy showed a sessile polyp measuring approximately 1 × 1 cm located 10 cm from the anus (Fig. 2B). Capsule endoscopic examination of the GI tract revealed dozens of blue vascular blebs with size ranging from 0.4 to 1 cm distributed from the jejunum to the ileum, and active bleeding in an ileal segment (Fig. 2C).

Based on clinical manifestation and capsule endoscopic investigation, the diagnosis of BRBNS was established. The patient underwent laparotomy with resection of lesions in the small intestine segment and was treated with iron supplementation for 3 months. Microscopic examination of the resected lesions showed multiple hemangiomas with hemorrhage and focal calcification in the submucosa (Fig. 1B). Postoperatively, the patient had an uncomplicated course. On follow-up after 3 years, she has remained free from blood transfusions with excellent vigor and her hemoglobin level has been maintained at 10.5 to 11 g/dL. In retrospect, the 2 pea-sized cutaneous nodules on the right opisthenar were likely consistent with venous malformations.

### 3. Discussion

The BRBNS was first reported by Gascoyen in 1860, and 100 years later Bean described it in detail; it is also called Bean’s syndrome. The estimated incidence of BRBNS is 1:14000 births. BRBNS lesions are often present at birth or appear in early childhood. Despite recent studies, the pathogenesis of this syndrome remains unclear. The majority of cases are sporadic, although several familial cases have been reported to be associated with chromosome 9p. The observation of c-kit on histologic analysis suggests that stem-cell factor/c-kit signaling may play a role in the constant growth of venous malformations. Additionally, the mammalian target of rapamycin complex might also be involved. Recently, Soblet et al discovered that somatic mutations in TEK (the gene encoding TIE2) could result in ligand-independent activation of TIE2 and lead to BRBNS. Our patient has no family history of BRBNS, and she did not undergo genetic testing due to poor economic conditions and our limited detection methods.

The clinical presentations of BRBNS vary according to the involvement of different organs. Vascular malformations are most common in the skin and GI tract, but virtually any tissue may be involved, including the central nervous system, liver, soft tissues, and so on. Usually, soft bluish bleb-like lesions, irregularly blue-stained macular lesions and deforming large lesions are the 3 types of lesions that can be identified in the skin of patients with BRBNS. Although the cutaneous lesions might vary from several to more than 100 distributing on the body surface, they are generally asymptomatic. Moreover, the presentation of cutaneous lesions may be delayed or occur without typical clinical manifestations, which may lead to a delay in diagnosis. In our case, the patient presented with only 3 lesions of the skin; 2 were resected before presenting to our outpatient department. For this reason, BRBNS was not initially suspected. It was reported that venous malformations of BRBNS can occur throughout the GI tract, but the small intestine is the most
common site. The most common symptoms with GI tract involvement are hemorrhage and secondary anemia due to digestive tract blood loss; however, some patients may rarely present with severe complications such as intussusception, rupture, gangrene, volvulus, and infarction. Here, we review all the published English literature concerning BRBNS with IDA from the Web of Science from the last 5 years, as summarized in Table 1. Among them, the minimum hemoglobin level was 2.2 g/dL and the longest duration of anemia before diagnosis was 11 years. With the exception of...
| Name                        | Age (y) | Gender (M/F) | Min Hb (g/dL)/course | Methods of detection of IDA | Involved organs | Treatment of BRBNS | Prognosis |
|-----------------------------|---------|--------------|----------------------|-----------------------------|-----------------|-------------------|-----------|
| Jin et al [3]               | 45      | F           | 3.6/5                | FOBT (+)                    | Skin, GI, oral mucosa, GI | Oral iron and blood transfusions | NR        |
|                            |         |              |                      | Hematochezia                |                 |                   |           |
|                            |         |              |                      | Upper and lower endoscopy   |                 |                   |           |
|                            |         |              |                      | Gastroscopy, capsule endoscopy |                 |                   |           |
|                            |         |              |                      | CT                          |                 |                   |           |
|                            |         |              |                      | CT                          |                 |                   |           |
| Goud et al [8]              | 76      | M           | 6.1/3                | FOBT (+)                    | Skin, GI, oral mucosa, GI | Oral iron and blood transfusions | NR        |
|                            |         |              |                      | Hematochezia                |                 |                   |           |
|                            |         |              |                      | Upper and lower endoscopy   |                 |                   |           |
|                            |         |              |                      | CT                          |                 |                   |           |
|                            |         |              |                      | CT                          |                 |                   |           |
| Doi et al [10]              | 6       | M           | 5.0/2                | FOBT (+)                    | Skin, joint, GI | Upper and lower endoscopy, capsule endoscopy | NR        |
|                            |         |              |                      | Hematochezia                |                 |                   |           |
|                            |         |              |                      | Upper and lower endoscopy   |                 |                   |           |
|                            |         |              |                      | CT                          |                 |                   |           |
|                            |         |              |                      | CT                          |                 |                   |           |
| Ucmak et al [9]             | 18      | F           | 6.7/3                | Gastroscopy                 | Skin, oral mucosa | Upper and lower endoscopy, capsule endoscopy | NR        |
|                            |         |              |                      | capsule endoscopy           |                 |                   |           |
|                            |         |              |                      | CT                          |                 |                   |           |
|                            |         |              |                      | CT                          |                 |                   |           |
| Grammatopoulos et al [11]   | 20      | F           | NR                   | FOBT (+), hematochezia       | GI, gingival area | Colonoscopy, capsule endoscopy | NR        |
|                            |         |              |                      |                             |                 |                   |           |
|                            |         |              |                      |                             |                 |                   |           |
| Lybecker et al [12]         | 10      | M           | 2.2/0.2              | None                        | Skin, tongue, chest | Colonoscopy, capsule endoscopy | NR        |
|                            |         |              |                      |                             |                 |                   |           |
|                            |         |              |                      |                             |                 |                   |           |
| Li et al [13]               | 10      | F           | 4.0/3                | FOBT (+)                    | GI, liver, liver | Upper and lower endoscopy | NR        |
|                            |         |              |                      | Hematochezia                |                 |                   |           |
|                            |         |              |                      | GI                          |                 |                   |           |
|                            |         |              |                      | GI bleeding                 |                 |                   |           |
|                            |         |              |                      | GI                          |                 |                   |           |
|                            |         |              |                      | CT                          |                 |                   |           |
|                            |         |              |                      | CT                          |                 |                   |           |
| Abraham et al [15]          | 24      | F           | 7.0/4                | None                        | Skin, GI        | Colonoscopy, capsule endoscopy | NR        |
|                            |         |              |                      |                             |                 |                   |           |
|                            |         |              |                      |                             |                 |                   |           |
|                            |         |              |                      |                             |                 |                   |           |

**Table 1**

**References**

1. Jin et al [3]
2. Goud et al [8]
3. Doi et al [10]
4. Ucmak et al [9]
5. Grammatopoulos et al [11]
6. Lybecker et al [12]
7. Li et al [13]
8. Abraham et al [15]

**Abbreviations**

- FOBT: Fecal occult blood test
- GI: Gastrointestinal
- Hb: Hemoglobin
- IDA: Iron deficiency anemia
- Min: Minimum
- NR: Not record
- SPECT: Single photon emission computerized tomography
- CT: Computed tomography
- DSA: Digital subtraction angiography

**Additional Notes**

- Two cases, all patients presented with typical cutaneous lesions. More importantly, all patients had clinical manifestation of hemorrhage including hematochezia, abdominal pain, melena, positive FOBT, and hemarthrosis. Our patient had refractory IDA for 10 years but denied melena, abdominal pain, hematochezia, or other hemorrhagic signs. Repeated FOBT was negative, and chest and abdomen CT showed no significant findings. Both gastroscopy and colonoscopy showed no lesions causing anemia. All of the above results lead to clinical confusion and failure to consider BRBNS. This case demonstrates that IDA can be the only symptom of GI lesions in BRBNS. Furthermore, lesions located in other organs may lead to relevant bleeding or compression symptoms.

- The diagnosis of BRBNS is based on clinical manifestations and is always established by characteristic lesions associated with GI bleeding. A series of reports revealed that non-invasive imaging modalities may often underestimate the number of lesions and suggest that video capsule endoscopy provides complete, direct, small-bowel examination of lesions. According to our review of the literature, upper and lower endoscopy can detect GI lesions in all patients. In our case, although the patient underwent enhanced abdominal CT, gastroscopy, and colonoscopy immediately, we did not identify lesions in the GI tract, and only after capsule endoscopy were the typical lesions and bleeding sites in the GI tract detected. Therefore, we advise comprehensive endoscopy including gastroscopy, colonoscopy, and capsule endoscopy in patients suspected of having GI bleeding due to BRBNS. Histologic examination of BRBNS lesions usually shows multiple, dilated venous malformations, lined by a single layer of thin endothelium, with surrounding thin connective tissue. However, the diagnosis of BRBNS is based on clinical findings; thus, biopsy is not routinely necessary. Additionally, BRBNS with cutaneous and GI tract involvement should be differentiated from Maffucci syndrome, Olsr–Weber–Rendu syndrome, and Klippel–Trenaunay–Weber syndrome.

- Currently, there is no consensus concerning the management of BRBNS, but we should create individualized treatment for patients based on the extent and severity of the disease. If patients only exhibit intermittent occult bleeding or mild anemia, conservative measures such as iron supplementation and blood transfusion are usually chosen and regular follow-up is also necessary. When patients present with massive hemorrhage, repeated severe anemia, or related GI complications, surgery or endoscopic treatment are recommended. Before surgical resection, appropriate evaluation of the number and location of lesions in the entire GI mucosa should be performed and overwhelming involvement may require staged operative treatment or consideration of alternative therapies. Endoscopic therapies of BRBNS have supplanted some surgical procedures with technical improvement and innovations, but may also be associated with a potential risk of ulcerations, strictures, and re-bleeding. Moreover, Yuksek-kaya et al first reported low-dose sirolimus (an antiangiogenic agent) has a significant effect on the treatment of BRBNS without any adverse drug reactions. Since the lesions of our patient are mainly concentrated in the jejunum and ileum, she underwent complete local excision where possible to avoid recurrence and to preserving bowel length. She was successfully treated with surgical resection, but further follow-up is still needed because incompletely resected or missed lesions may enlarge and cause symptoms. Most patients with BRBNS have good prognoses and can survive with this disease, but the
quality of life declines due to GI bleeding and requirement for blood transfusions.[3]

4. Conclusion
The evaluation of children presenting with anemia of unknown origin requires an open mind so as not to miss any rare causes, including a high index of suspicion for BRBNS. Typical cutaneous lesions combined with adequate endoscopy can augment the accuracy of diagnosis and improve the patients’ quality of life.

Author contributions
Conceptualization: Ju Gao.
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