International Journal of Clinical Medicine & Pharmacology

https://doi.org/10.70731/s2hbdt59

Two Cases of Maxillofacial Vascular Malformations Associated with Blue Rubber Bleb Nevus Syndrome And Literature Review

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KEYWORDS

Maxillofacial Vascular Malformations,
Blue Rubber Bleb Nevus Syndrome,
Gastrointestinal Vascular Malformations,
Clinical Diagnosis and Treatment,
Case Report

ABSTRACT

Blue Rubber Bleb Nevus Syndrome (BRBNS) is a rare systemic vascular malformation-related disorder that primarily affects the skin, gastrointestinal tract, and central nervous system. Approximately 55.9% of patients have lesions involving the oral and maxillofacial region. Due to the potential risks of gastrointestinal hemorrhage and intracerebral hemorrhage, it is crucial for dental practitioners to promptly identify and refer such cases to relevant departments to improve patient prognosis and enhance quality of life. This paper reports two cases of BRBNS associated with maxillofacial vascular malformations treated at the Oral and Maxillofacial Surgery Department of Henan Provincial People's Hospital. In conjunction with a literature review, this study discusses the clinical features, diagnosis, and treatment strategies of BRBNS, aiming to raise awareness among dental practitioners to avoid missed or incorrect diagnoses.

1. Introduction

Blue Rubber Bleb Nevus Syndrome (BRBNS) is a rare systemic vascular malformation disorder that primarily affects the skin, gastrointestinal tract, and central nervous system. It is characterized by multiple vascular malformations in the skin and digestive system, with clinical manifestations commonly including multiple cutaneous vascular malformations, gastrointestinal bleeding, and secondary iron-deficiency anemia(Martinez et al., 2014).

The distribution of BRBNS lesions varies among patients. According to a study by Kozai L et al., the most commonly affected site is the oral cavity (55.9%), followed by the small intestine (49.5%), colorectum (35.6%), and stomach (26.7%) (Kozai & Nishimura, 2023). This indicates that some BRBNS

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Received 12 December 2024; Received in revised form 25 December 2024; Accepted 2 January 2025; Available online 16 January 2025.

patients may initially present to the dental department due to maxillofacial vascular malformations.

Given this, the present study reports two cases of BRBNS with maxillofacial vascular malformations as the primary clinical presentation, which were diagnosed and treated at the Department of Oral and Maxillofacial Surgery, Henan Provincial People's Hospital. A review of the relevant literature is also provided to discuss the clinical features, diagnostic criteria, and treatment strategies for BRBNS. The aim is to raise awareness among dental practitioners, reduce the risk of missed or misdiagnosed cases, and ultimately improve patient outcomes.

Both cases reported in this study obtained informed consent from the patients or their guardians. The study protocol was reviewed and approved by the Ethics Committee of the School of Medicine, Henan University (Approval No. HUSOM2024-452).

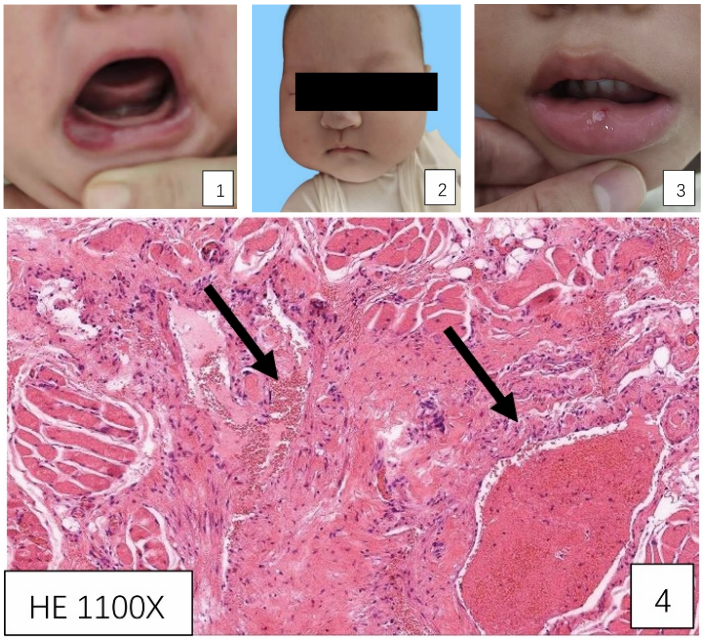


Figure 1-4

1. Right lower lip; 2. Nasal tip; 3. Central lower lip; 4. Microscopic view showing dilated lumens of varying sizes, with possible thrombus formation within the lumens.

2. Patients

2.1. Case 1

A 3-month-old male infant presented with a chief complaint of "red-blue masses on the nasal tip and right lower lip for over one month." The parents noticed the appearance of red-blue discoloration and localized swelling on the nasal tip and the right lower lip, which showed no significant improvement after one month of observation, prompting them to seek medical attention.

Physical examination revealed a red-blue soft mass measuring approximately 1.5 × 1.5 × 1 cm on the nasal tip and another on the right lower lip measuring 1.5 × 1 × 0.5 cm (Figures 1, 2). Both lesions were soft in texture, homogeneous, and non-hemorrhagic. The patient had no family history of hereditary diseases.

Upon admission, routine blood tests revealed hemoglobin levels of 117.3 g/L, while fecal occult blood test (FOBT) was weakly positive. No other abnormalities were detected in the standard laboratory workup. Abdominal computed tomography (CT) revealed no significant abnormalities.

A multidisciplinary discussion (MDT) was held involving specialists from oral and maxillofacial surgery, pediatric surgery, gastroenterology, and vascular anomaly departments. The initial diagnosis was multiple vascular malformations of the maxillofacial region, with the possibility of Blue Rubber Bleb Nevus Syndrome (BRBNS) not being excluded. The patient's family was informed of the condition, and oral iron supplementation was recommended to correct anemia. Although endoscopic examination of the gastrointestinal tract was suggested, the procedure was deemed too risky due to the patient's young age. The parents opted for surgical treatment of the mass on the right lower lip only.

Under general anesthesia, a "right lower lip mass excision" was performed. Postoperative histopathological examination revealed features consistent with venous malformation with thrombosis (Figure 4). The patient was treated with oral iron supplements following surgery and was followed up at 1, 3, and 6 months postoperatively. No recurrence of the mass was observed, and the patient's hemoglobin levels gradually increased from 136.8 g/L to 143.9 g/L.

Two years after surgery, a new mass reappeared on the patient's lower lip (Figure 3). The patient was referred to a pediatric specialist hospital for gastrointestinal endoscopic examination. Endoscopy revealed hemorrhagic and bluish lesions in the small intestinal wall. The lesions were excised, and hemostasis was achieved via ligation. Histopathological analysis confirmed venous malformation, leading to a definitive diagnosis of BRBNS.

The lesions on the lower lip and nasal tip were treated with local injections of pingyangmycin, a sclerosing agent. One year after treatment, follow-up re-

vealed that the patient had normal hemoglobin levels, a negative fecal occult blood test (FOBT), and significant reduction in the size of the masses on the lower lip and nasal tip.

2.2. Case 2

A 14-year-old male patient was referred to our hospital with a chief complaint of "bilateral temporal masses for 10 years and a tongue mass for 1 year."

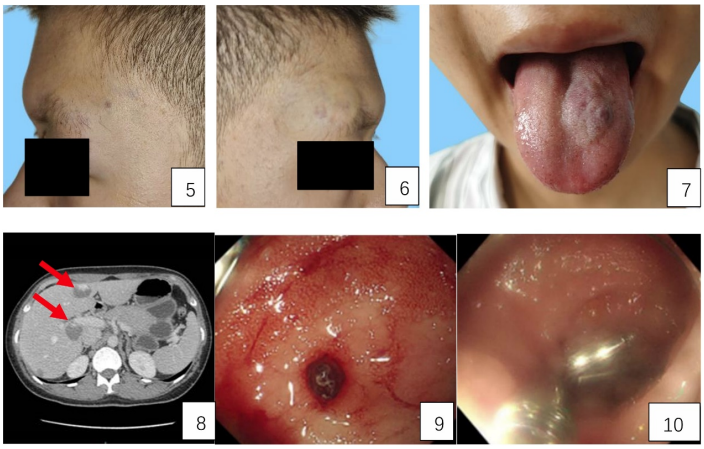
Physical examination revealed multiple bluish-purple masses on both temporal regions and the dorsal surface of the left side of the tongue (Figures 5-7). The masses were soft in texture, with no signs of bleeding, ulceration, or significant tenderness. The patient had a history of chronic anemia and had previously received treatment with traditional Chinese herbal decoctions at a local clinic, with limited therapeutic effect. There was no family history of hereditary diseases.

Upon admission, routine blood tests revealed a white blood cell count of 9.59 × 10^9/L and hemoglobin level of 104.1 g/L. The fecal occult blood test (FOBT) was weakly positive, while other routine laboratory tests were unremarkable. Abdominal computed tomography (CT) suggested the presence of multiple hepatic hemangiomas (Figure 8).

A multidisciplinary team (MDT) composed of specialists from oral and maxillofacial surgery, gastroenterology, spinal surgery, and vascular anomaly departments convened to discuss the case. The initial diagnosis was Blue Rubber Bleb Nevus Syndrome (BRBNS). Endoscopic examination of the gastrointestinal tract revealed bleeding at the terminal ileum, for which an endoscopic hemostasis procedure was performed (Figures 9, 10). The biopsy results confirmed the diagnosis of BRBNS.

The patient underwent local sclerotherapy with pingyangmycin injections targeting the masses in the bilateral temporal regions and the tongue. Following treatment, the patient's condition improved, and he was discharged from the hospital.

Follow-up visits were conducted at 1, 2, and 3 months post-discharge. Significant reduction in the size of the masses on the bilateral temporal regions and tongue was observed, and the patient received additional local sclerotherapy with pingyangmycin injections during this period. At 3 months post-discharge, the patient's overall health continued to improve. His hemoglobin level increased to 109.3-126.5 g/L, and the fecal occult blood test (FOBT) turned negative. At 6 months and 1 year post-discharge, follow-up evaluations revealed no recurrence of anemia, normal blood test results, and persistently negative FOBT.



Figures 5-10

5. Vascular malformation in the left temporal region; 6. Vascular malformation in the right temporal region; 7. Vascular malformation on the dorsal surface of the left side of the tongue; 8. CT showing multiple hepatic hemangiomas; 9. Active thrombus head observed at the terminal ileum;10. Thrombus head closed with metal clips.

3. Discussion

3.1. Etiology

Blue Rubber Bleb Nevus Syndrome (BRBNS) was first described by Gascoyen in 1860(Gascoyen, n.d.). Later, in 1958, Bean provided a detailed description of its clinical features and officially named it Blue Rubber Bleb Nevus Syndrome (also known as Bean Syndrome)(Bean, 1958). To date, more than 400 cases of BRBNS have been reported in the literature. However, the exact etiology and pathogenesis of this disorder remain incompletely understood.

Recent advances in molecular genetics have provided new insights into the etiology of BRBNS. Studies have suggested that BRBNS may be closely associated with mutations in the TEK gene (also known as the TIE2 gene) (Nobuhara et al., 2006). Mutations in the TEK gene can lead to abnormal proliferation and migration of vascular endothelial cells, ultimately resulting in vascular malformations. Additionally, upregulation of c-kit expression has been observed in some BRBNS patients. Researchers hypothesize that c-kit plays a pivotal role in the pathogenesis of BRBNS, and specific inhibitors of c-kit may provide a nov-

el targeted therapeutic approach for the treatment of this disease (Mogler et al., 2010).

The majority of BRBNS cases are sporadic, with no family history of the disease. However, in rare cases, family-based studies have revealed a potential association between mutations on the short arm of chromosome 9 (9p) and BRBNS, suggesting that it may exhibit characteristics of autosomal dominant inheritance (Gallione et al., 1995). This finding implies that BRBNS may have a genetic predisposition in certain families, but large-scale genome-wide association studies (GWAS) have yet to identify specific pathogenic genes.

Research on the pathogenesis of BRBNS is ongoing, and the potential role of genetic-epigenetic interactions is drawing increasing attention. Whether signaling pathways associated with the TEK gene and c-kit (such as the PI3K-Akt pathway) play a key role in the pathogenesis of BRBNS remains to be elucidated. Furthermore, the potential role of external environmental factors and molecular epigenetic modifications in the onset and progression of BRBNS is another area of interest. Future studies on these mechanisms may offer new insights into disease development and therapeutic strategies.

3.2. Clinical Manifestations

The clinical manifestations of Blue Rubber Bleb Nevus Syndrome (BRBNS) are diverse, with the most prominent features being vascular malformations of the skin and gastrointestinal tract. According to a statistical analysis of 106 BRBNS cases reported by RIMONDI A et al., 57.5% of patients develop symptoms before the age of 18 (Rimondi et al., 2024). The two cases reported in this study, involving a 3-month-old infant and a 14-year-old adolescent, are consistent with these findings.

BRBNS-related cutaneous lesions typically present as multiple bluish-purple, rubber-like blebs distributed across the body. These lesions are soft and compressible, and upon compression, they flatten temporarily but rebound quickly after pressure is released (Chen et al., 2022). While the cutaneous lesions of BRBNS generally do not cause bleeding or other life-threatening conditions, and no reports of malignant transformation have been published to date, these lesions can affect a patient's appearance, leading many patients to seek medical attention for cosmetic reasons.

A retrospective study by RIMONDI A et al. reported that more than 50% of patients with BRBNS underwent multiple treatments during the disease course (Rimondi et al., 2024), reflecting the long-term treatment needs associated with this condition.

BRBNS-related gastrointestinal (GI) lesions are most frequently observed in the stomach and intestines, where they appear as multiple vascular malformations. The primary clinical manifestation is recurrent gastrointestinal bleeding, which is also a major cause of anemia in these patients. Other symptoms include abdominal pain and discomfort (da Fonseca et al., 2009). Due to the extensive distribution of vascular malformations in the gastrointestinal tract, some patients may experience acute complications such as intussusception, volvulus, or bowel infarction (Wang et al., 2014).It is worth noting that mild symptoms, such as mild anemia or positive fecal occult blood test (FOBT), often go unnoticed by patients or their families. This can lead to delays in diagnosis and treatment, particularly in patients without obvious gastrointestinal bleeding.

In addition to the skin and gastrointestinal tract, BRBNS can also affect multiple organs and systems, including the liver, spleen, heart, eyes, and central nervous system (CNS) (R et al., 2014).When the CNS is involved, patients may present with headaches (R et al., 2014), seizures [14], or even intracranial hemorrhage (G et al., 2010), which are serious and potentially life-threatening complications.

Other uncommon systemic manifestations include pain (5%) and localized hyperhidrosis (2%) (McCarthy et al., 1982). When the disease affects the joints, patients may develop movement disorders or, in severe cases, joint deformities, which can significantly impact their quality of life (McCarthy et al., 1982).

The histopathological features of BRBNS lesions are typically consistent with venous malformations and cavernous venous dilation. Under the microscope, the affected areas show a simple layer of endothelial cells lining a thin layer of smooth muscle cells (Hasosah et al., 2010). This distinctive histopathological profile provides important clues for disease identification and diagnosis.

The diagnosis of BRBNS relies on a combination of physical examination and gastrointestinal endoscopy. The presence of typical cutaneous lesions is often sufficient to raise clinical suspicion. Gastrointestinal endoscopy can reveal characteristic vascular malformations in the gastrointestinal tract, confirming

the diagnosis.In most cases, biopsy for diagnostic purposes is not necessary, as the combined evidence from clinical presentation and endoscopic findings is sufficient for diagnosis (Atten et al., 2000).

3.3. Clinical Diagnosis

The diagnosis of Blue Rubber Bleb Nevus Syndrome (BRBNS) primarily relies on clinical examination, especially the identification of characteristic lesions in the skin, oral cavity, and gastrointestinal tract. The typical bluish-purple, rubber-like blebs on the skin often serve as early diagnostic clues for BRBNS. Lesions in the oral and maxillofacial regions also provide additional diagnostic support, especially in patients with facial abnormalities or oral ulcers.

Endoscopy is considered the gold standard for both the diagnosis and treatment of BRBNS(Nishiyama et al., 2012), particularly for the evaluation and management of gastrointestinal vascular malformations. Among the available endoscopic methods, capsule endoscopy (CE) has become an effective tool for evaluating small intestinal lesions due to its non-invasiveness, good patient tolerance, and high acceptance rate (Barlas et al., 2008; Kassarjian et al., 2003; Kopácová et al., 2007).

Compared with balloon-assisted enteroscopy (BAE), capsule endoscopy is simpler to operate and more acceptable to patients, especially for children and those who are unable to tolerate conventional endoscopy.Endoscopic examination not only plays a role in diagnosis but also facilitates endoscopic hemostasis and lesion resection. For instance, in cases of bleeding from the terminal ileum, endoscopic hemostasis can significantly improve the patient's prognosis.

In the initial screening for BRBNS, the fecal occult blood test (FOBT) serves as a simple and cost-effective screening tool, particularly for patients without obvious signs of gastrointestinal bleeding. The FOBT can detect occult gastrointestinal bleeding, even when the volume of blood loss is small.Given that recurrent gastrointestinal bleeding is one of the major clinical manifestations of BRBNS, a positive FOBT result is often an important early clue for diagnosing the disease. Therefore, for patients with chronic anemia or a history of gastrointestinal bleeding, FOBT should be considered a routine screening test.

Imaging examinations play a crucial role in localizing lesions and assessing the extent of disease in patients with BRBNS.Computed Tomography (CT) scans provide clear visualization of lesions in the gastrointestinal tract and abdominal solid organs, such as multiple hepatic hemangiomas. CT is also useful for assessing the number, size, and distribution of lesions (Agnese et al., 2010). Furthermore, CT scans play an important role in the detection of acute complications, such as intussusception, volvulus, and bowel infarction, which may require immediate medical intervention.

Compared with CT, Magnetic Resonance Imaging (MRI) has higher soft-tissue resolution, making it more effective for the detailed assessment of soft-tissue lesions. MRI is particularly useful in the evaluation of lesions in the central nervous system (CNS) and in determining the extent and depth of vascular abnormalities. For the liver, spleen, and other parenchymal organs, MRI has a higher sensitivity than CT (Certo et al., 2007). This makes MRI a valuable tool for identifying small or subtle lesions that may be missed on CT scans.

3.4. Clinical Treatment

Currently, there is no unified, systematic treatment guideline for Blue Rubber Bleb Nevus Syndrome (BRBNS). Clinical treatment strategies are primarily based on the patient's clinical presentation and specific symptoms, employing an individualized, symptom-targeted approach. Oral and cutaneous lesions generally do not require special treatment; however, if lesions affect aesthetics or local function, local treatments such as sclerotherapy, laser therapy, or surgical resection may be considered (Dwivedi & Misra, 2002).

For oral and cutaneous BRBNS lesions, the primary treatment goals are to restore appearance and local function. The injection of bleomycin, polidocanol, or absolute ethanol into the lesion can induce local fibrosis and vascular occlusion, leading to lesion shrinkage or regression (Dwivedi & Misra, 2002). Pulsed dye laser (PDL) or Nd:YAG laser can reduce the size of cutaneous lesions, thereby improving appearance. For localized or recurrent lesions, surgical resection is a direct and effective treatment. However, surgery carries a higher risk of trauma, and there is a possibility of lesion recurrence after the procedure.

The treatment of gastrointestinal (GI) lesions depends on the number, size, shape, location, and bleeding status of the vascular malformations. Treatment strategies generally include endoscopic, interventional, and surgical approaches. In this study,

Case 1 underwent an "endoscopic hemostasis procedure for gastrointestinal bleeding," which achieved satisfactory hemostatic results. This method plays a crucial role in controlling acute GI bleeding. Injection of absolute ethanol or polidocanol into the lesion under endoscopy can occlude abnormal blood vessels, achieving hemostasis (Dieckmann et al., 1994). High-frequency electrocoagulation or laser energy can directly seal abnormal blood vessels, making it particularly suitable for diffuse lesions and small vascular abnormalities. Embolization therapy involves the injection of embolic agents (e.g., gelatin sponge or microparticle embolic agents) into the affected vessels via an interventional catheter, enabling precise occlusion of blood supply to the lesion (Jin et al., 2014). Embolization therapy serves as a supplementary method for endoscopic treatment, especially for severe GI bleeding from deep small bowel lesions.

Surgical treatment is typically a last-resort option, mainly used for cases where endoscopic and interventional therapies are ineffective. Indications for surgery include localized lesions, such as focal lesions in the stomach or small intestine; massive GI bleeding that is unresponsive to endoscopic treatment; and acute complications such as bowel ischemia, intussusception, and intestinal infarction (Choi et al., 2012). However, surgery is associated with higher trauma and recurrence rates, so the risks and benefits must be weighed carefully. Endoscopic or interventional therapy is generally preferred, and surgery is reserved for life-threatening situations.

The goal of pharmacological treatment is to control GI bleeding and disease progression by reducing endothelial cell proliferation and angiogenesis. Commonly used drugs include Glucocorticoids: Prednisone can inhibit inflammation and endothelial cell proliferation, providing temporary symptom relief for certain patients (Dieckmann et al., 1994).

Interferon-α: This agent modulates immune responses and inhibits angiogenesis, showing efficacy in some refractory cases, but its adverse effects are significant.

Vincristine: As an anti-mitotic agent, it reduces endothelial cell proliferation. However, its clinical use is limited by adverse effects such as bone marrow suppression (Aihara et al., 1991).

Octreotide: As a somatostatin analog, it reduces visceral blood flow, thereby decreasing the frequency of GI bleeding (Boente et al., 1999).

In recent years, sirolimus (rapamycin) has emerged as a breakthrough drug for BRBNS treatment. Sirolimus, an mTOR pathway inhibitor, reduces venous malformation size and controls GI bleeding by inhibiting endothelial cell proliferation and angiogenesis (Gonzalez-Magaña et al., 2024; Pi et al., 2023).

According to a retrospective study by Quan Xu et al. on 26 BRBNS patients treated with sirolimus, all patients experienced significant clinical improvement, with no severe drug-related adverse reactions. The adverse effects of sirolimus are relatively mild, mainly including oral ulcers, rashes, and mild liver function impairment. Its high safety profile and good patient compliance make it a promising option for children and refractory cases.

With the advancement of pharmacological and interventional therapies, multidisciplinary individualized treatment (MDT) has become the standard treatment strategy for BRBNS. MDT treatment plans can be customized based on the severity of the patient's symptoms, lesion location, and treatment risk. For GI lesions, endoscopic treatments (e.g., hemostasis, laser coagulation) are generally the first-line options. When multiple endoscopic treatments fail, interventional therapy or surgical treatment may be considered.

4. Conclusion

As the starting point of the digestive tract, oral involvement in Blue Rubber Bleb Nevus Syndrome (BRBNS) accounts for up to 55.9% of cases (Kozai & Nishimura, 2023). However, due to insufficient awareness of this disease among oral clinicians, detailed auxiliary examinations are often overlooked, leading to missed or incorrect diagnoses. This delay in diagnosis hampers early detection, timely treatment, and prognosis improvement, while also increasing the risk of emergency medical events.

Although BRBNS is a rare disorder, patients face an ongoing risk of life-threatening gastrointestinal (GI) bleeding and cerebral hemorrhage. For patients presenting with multiple vascular malformations across the body or a history of multiple vascular malformation treatments, physicians should maintain a high degree of vigilance. A detailed medical history should be obtained, especially focusing on symptoms of gastrointestinal bleeding and a history of anemia. In such cases, routine blood tests and fecal occult blood tests should be conducted to assess for the presence of anemia or GI bleeding. If clear indications of anemia or GI bleeding are identified, further diagnostic imaging, including gastrointestinal endoscopy, abdominal

and cranial CT scans, and abdominal ultrasound, should be performed to determine the presence of vascular malformations in other systems.

Once a diagnosis of BRBNS is confirmed, a multidisciplinary team (MDT) consultation involving specialists from gastroenterology, pediatric surgery, pathology, and vascular anomaly units should be convened. This collaborative approach aims to develop an individualized treatment strategy. If necessary, the patient should be referred to a specialized department, such as gastroenterology or vascular anomaly centers, for further treatment. Early detection and timely intervention for vascular malformations in the gastrointestinal system, nervous system, or other organs can alleviate patient suffering, reduce the occurrence of emergency medical events, and improve both prognosis and quality of life.

Oral and maxillofacial surgeons often encounter patients with vascular malformations or masses in the head, neck, and oral cavity. It is essential to differentiate BRBNS from other syndromes associated with vascular malformations, including Osler-Weber-Rendu syndrome (hereditary hemorrhagic telangiectasia, HHT), Klippel-Trenaunay syndrome, and Maffucci syndrome (Choi et al., 2012; Marín-Manzano et al., 2010). While these conditions share the feature of vascular anomalies, they present distinct clinical manifestations and diagnostic criteria.

Osler-Weber-Rendu syndrome (HHT) is characterized by punctate hemorrhagic telangiectasia, recurrent epistaxis, and capillary dilatation, often with a positive family history (Gallo & McClave, 1992; Shovlin et al., 2000).Maffucci syndrome typically presents with diffuse vascular malformations of the skin and soft tissues, skeletal deformities, and enchondromas (Sakurane et al., 1967; Shepherd et al., 2005).Klippel-Trenaunay-Weber syndrome is primarily characterized by venous varicosities, soft tissue and bone hypertrophy, and limb enlargement (Arguedas et al., 2001).

In summary, the hallmark clinical features of BRBNS include multiple vascular malformations of the skin and oral cavity, as well as gastrointestinal bleeding, which frequently results in iron deficiency anemia (IDA). To date, there is no universally accepted systematic treatment guideline for BRBNS. This study aims to raise awareness of BRBNS among oral clinicians to prevent misdiagnosis and missed diagnoses. Based on the analysis of this case, clinicians should consider the possibility of BRBNS when patients present with multiple vascular malformations in the maxillofacial region and other parts of the body, especially if they have a positive fecal occult blood test or a history of anemia. Early diagnosis and timely intervention are essential to prevent emergency medical events, improve prognosis, and enhance patients' quality of life.

Conflict of Interest

None declared.

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