CASE REPORT

Blue rubber bleb naevus syndrome: a rare cause of chronic occult blood loss and iron deficiency anaemia

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SUMMARY

Blue rubber bleb naevus syndrome (BRBNS) is a rare vascular disorder with malformed veins, or blebs, appearing in the skin or internal organs. Gastrointestinal tract involvement is the most common feature and often subject to bleeding, potentially resulting in chronic occult blood loss and iron deficiency anaemia. We present the case of a 10-year-old boy with venous malformations on the feet and severe anaemia. Although massive sudden haemorrhage rarely occurs, awareness of the illness is necessary to prevent complications.

BACKGROUND

Blue rubber bleb naevus syndrome (BRBNS) is a rare vascular disorder in which malformed veins, or blebs, appear in the skin or internal organs. The syndrome is named due to the distinctive appearance of cutaneous lesions, which are soft, blue, compressible veins that become wrinkled when blood is expressed.¹

The incidence of this syndrome is low, and <200 cases have been described in the literature.² The most common presentation is sporadic cases, although an autosomal dominant mode of inheritance has been observed with linkage to a locus on chromosome 9p.³ The pathogenesis is not fully established, but tyrosine kinase is suspected to play a role.⁴

Cutaneous lesions are usually present at birth or during early childhood and mostly located on the tongue, face, trunk and extremities.⁵ Although often asymptomatic, lesions may exhibit tenderness to palpation or hyperhidrosis in the overlying skin.⁶

The gastrointestinal tract is the most common organ system affected by BRBNS, particularly the small bowel and distal colon.⁷ Case reports have also demonstrated involvement of the central nervous system, eyes, oral cavity, thyroid, parotid gland, musculoskeletal system, lungs, kidney, liver, spleen and bladder.⁸

The most common clinical presentation is acute or chronic bleeding from gastrointestinal lesions, requiring transfusion and iron replacement therapy. Infrequent complications are intussusception of part of the bowel, bowel infarction and skeletal bowing.^{8–10}

CASE PRESENTATION

A 10-year-old boy presented with a history of multiple venous malformations on the feet, fatigue, paleness and intermittent abdominal pain. The patient had suffered from the anaemia for

2 months and due to shortness of breath and rapid heartbeat had increased trouble keeping up with friends during sports. Blood cell count revealed iron deficiency anaemia (haemoglobin 2.2 mmol/L, P-iron <2 µmol/L, P-ferritin 3 µg/L). No haematemesis, melena or rectal bleeding had been observed. Cutaneous examination revealed multiple blue papules on the soles of the feet ranging from 2 to 10 mm in diameter. A single blue papule was noted close to the left eyelid.

There was no known family history of vascular disorder and no obvious abnormality was recorded at birth. At the age of 3 months, blue papules with definite boundaries had appeared on the feet. At the age of 10, additional papules appeared on the right hand and left distal crus. The papules were painful during compression and showed alternating growth and remission in 4-week to 6-week cycles.

INVESTIGATIONS

Upper gastrointestinal endoscopy revealed no sign of vascular malformation or recent bleeding. Colonoscopy showed 20 vascular malformations in the colon (figure 1). Six additional vascular malformations were found by capsule endoscopy in the small bowel.

The diagnosis of BRBNS was established based on clinical history, characteristic physical appearance of the cutaneous lesions, and the pathognomonic endoscopic appearance of the gastrointestinal lesions.

If BRBNS is suspected, a comprehensive assessment of any vascular malformations in other organs is warranted. Gastrointestinal staging should

Figure 1 Vascular lesions identified by colonoscopy. Characteristic of blue rubber bleb naevus syndrome.

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include upper gastrointestinal endoscopy, video capsule endoscopy and colonoscopy. MRI is a beneficial tool to depict the involvement of bones, joints, liver, spleen and pancreas. In addition, labelled red blood cell nuclear scans can be used to localise site of bleeding in patients presenting with gastrointestinal haemorrhage and negative endoscopy results.¹¹

TREATMENT

The medical literature on the treatment of BRBNS is currently limited to case reports. Since cutaneous lesions rarely bleed, treatment is seldom needed unless these are cosmetically unacceptable or functionally troublesome.

No curative therapy is currently available for the gastrointestinal lesions, although different therapeutic strategies have been proposed. The choice of different treatment modalities depends on number of lesions, location and size. In most patients treatment is symptomatic and consists of lifelong iron replacement and frequent blood transfusions in cases with severe anaemia.^{8 9} Pharmacological agents have recently been reported to induce remission of gastrointestinal lesions. Unfortunately, adverse drug reactions may occur and discontinuing administration of medical treatment may lead to symptom recurrence.¹² Endoscopic interventions, such as band ligation, sclerotherapy and laser coagulation have also been used to control gastrointestinal bleeding, but only in case reports and without evidence of sustained success.¹³ Complications of endoscopic interventions include development of ulcerations and strictures.

OUTCOME AND FOLLOW-UP

The patient received blood transfusion and started oral iron replacement therapy and subsequently long-term sirolimus treatment to obtain clinical remission. According to instructions given, a starting per oral dose of 3 mg sirolimus was given once daily with the aim of reaching the target area of 4 µg/L. The dose of sirolimus was quickly reduced to 2 mg daily due to the presence of elevated sirolimus levels in the blood. The dose reduction achieved levels in the target area.

The pain subsided within a few days after initiation of sirolimus and the patient could again participate in sports. No other medical or endoscopic interventions were made before sirolimus treatment.

We followed our patient in monthly intervals in our outpatient clinic and regularly assessed sirolimus blood levels and surveillance tests, consisting of complete blood cell count, analysis of plasma proteins and lipid status.

Three months after sirolimus was introduced, the patient remained in good clinical condition with stable, normal haemoglobin. There was no need for repeated blood transfusions and no adverse drug reactions or complications were observed. The papules on the feet regressed in size and ceased being painful during compression. Reassessment upper and lower gastrointestinal endoscopy was performed and revealed only 2 remaining vascular malformations in the small bowel and 10 in the colon. All of the remaining malformations appeared regressed in size.

For the moment the patient is still on sirolimus and we plan to continue the therapy for a year and then taper gradually over 3 months. In case of signs of disease recurrence sirolimus or another mechanistic target of rapamycin (mTOR) inhibitor will be recommended.

DISCUSSION

In the present case, the patient was treated with sirolimus, an immunosuppressant with antiangiogenic properties. Shortly after initiation of sirolimus and blood transfusion, a spectacular

improvement in the patient's condition was observed and clinical remission obtained. Recent studies have also reported successful sirolimus treatment in patients with BRBNS without adverse effects or recurrence of symptoms on withdrawal.^{14–17}

Sirolimus has potential adverse effects on bone marrow, renal functions and cholesterol metabolism. In addition, immunosuppression from sirolimus may lead to an increased susceptibility to infection and possible development of neoplastic disease, especially lymphoma. Hence, patients should be monitored closely including physical examination and blood test.

Nevertheless, despite the potential side effects, the use of sirolimus seems more reasonable than the use of surgical treatment especially in patients with multiple lesions. Although, some patients with few lesions may benefit from endoscopic therapy alone. The role of surgical resection in the management of gastrointestinal lesions is contentious, since recurrence of lesions after surgical treatment has been reported.^{6 8} The recurrence rate, although rare, should be interpreted in the context of the few published cases of BRBNS. Consequently, surgical resection should be reserved for patients with a recurrent need for blood transfusion or in patients with adverse drug reactions.¹⁸

This case is presented for rarity, and awareness of the illness is necessary to prevent complications. Furthermore, this case suggests that sirolimus treatment is effective and safe and should be considered as a viable medical treatment for BRBNS. Owing to the risk of adverse effects, serum levels should be monitored and patients made aware of the predisposition to infection. The issue whether sirolimus can be discontinued without symptom recurrence is currently being investigated and studies with longer follow-up are warranted.

Learning points

- ▶ Blue rubber bleb naevus syndrome (BRBNS) is a rare vascular disorder with malformed veins, or blebs, appearing in the skin or internal organs.
- ▶ Gastrointestinal tract involvement is the most common feature and often subject to bleeding, potentially resulting in chronic occult blood loss and iron deficiency anaemia.
- ▶ When BRBNS is suspected, a comprehensive assessment of any vascular malformations in other organs is warranted including upper gastrointestinal endoscopy, video capsule endoscopy, colonoscopy and MRI.
- ▶ Sirolimus treatment should be considered as a viable medical treatment for BRBNS.

Competing interests None declared.

Patient consent Obtained.

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