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NOTE

The blue rubber bleb nevus syndrome co-existing with celiac disease

J.J. Oosterheert[1*], M.T. Bousema[2], J. Lagendijk[3], M.H.H. Kramer[1]

Departments of [1]Internal Medicine, [2]Dermatology and [3]Pathology, Meander Medical Centre, PO Box 1502, 3800 BM Amersfoort, the Netherlands, [*]corresponding author: tel.: +31 (0)33-850 24 44, fax: +31 (0)33-850 48 63, e-mail: J.J.Oosterheert@gmail.com

ABSTRACT

Background: Anaemia caused by iron deficiency is one of the most common disorders in the world. We describe a patient with iron deficiency anaemia in whom absorption was limited due to celiac disease, superimposed to chronic blood loss due to the blue rubber bleb nevus syndrome, a rare syndrome characterised by multiple cutaneous venous malformations in association with visceral lesions.
Case report: A 54-year-old patient with severe iron deficiency anaemia showed marked rubbery cutaneous lesions on the body surface, extremities, under and on the left side of the tongue as well as in the stomach and duodenum. The appearance and pathological examination of the lesions were consistent with the diagnosis of blue rubber bleb nevus syndrome (BRBNS). Biopsy of the mucosa of the duodenum showed celiac disease. No association between celiac disease and BRBNS has been previously described.
Conclusion: Combined loss of iron and malabsorption from the gastrointestinal tract can lead to severe iron deficiency. Early recognition of both diseases can result in early treatment. Patients can recover completely with iron suppletion and a gluten-free diet. Recognising typical BRBNS skin lesions would provide a potential diagnosis and could prevent unnecessary procedures or invasive surgery.

KEYWORDS

Blue rubber bleb nevus syndrome, celiac disease, iron deficiency anemia

INTRODUCTION

Anaemia caused by iron deficiency is one of the most common disorders in the world. The World Health Organisation estimates that more than 30% of the population suffer from iron deficiency anaemia (http://www.who.int/nut/ida.htm). Causes of iron deficiency include an increased demand for iron e.g. in pregnancy, an increased iron loss, e.g. chronic blood loss from the gastrointestinal tract, or decreased iron intake, absorption or use, e.g. such as resulting from an inadequate diet. In this report, we describe a patient with severe iron deficiency anaemia, in whom absorption was limited due to the presence of celiac disease, superimposed to chronic blood loss from the gastrointestinal tract due to the blue rubber bleb nevus syndrome, a rare syndrome characterised by multiple cutaneous venous malformations in association with visceral lesions, affecting predominantly the gastrointestinal tract.

CASE REPORT

A 54-year-old female patient was evaluated because of iron deficiency anaemia. Medical history included an unconfirmed encephalitis at the age of 6, a pulmonary abnormality which possibly resulted in a pulmonary haemorrhage when she was 23 years, and periods of iron deficiency anaemias for which she had received multiple courses of iron suppletion. She developed a hemiparesis at the age of 43, after an episode of atrial fibrillation. Her last menstrual bleeding had occurred ten years ago. On presentation, she complained of painful rhagades in the corners of her mouth, which had not healed despite the use of several topical applicants. Her defecation occurred twice daily and consisted of loose stools. There was no obvious blood loss, and her weight was stable at 59 kg. On examination, there were marked rubbery cutaneous lesions on the body surface of the trunk and on the extremities (*figure 1*). Similar lesions were found under and on the left side of the tongue.
Laboratory examination revealed a microcytic anaemia with a haemoglobin level of 4.4 mmol/l and mean corpuscular volume of 62 fl. Serum iron concentration was 2 mmol/l

with a ferritin level of 4 µg/l consistent with the diagnosis of anaemia caused by iron deficiency.

On gastroscopy, angiodysplastic lesions were found in stomach and duodenum (*figure 2*). Biopsy of the mucosa of the duodenum showed a picture of gluten-induced enteropathy grade III, according to the modified Marsh criteria, consistent with the diagnosis of celiac disease.[1]

Cutaneous biopsy of a lesion on the trunk showed vascular proliferations, suspicious of arteriovenous malformation (*figure 3*). The appearance and pathological examination of the lesions were consistent with the diagnosis of blue rubber bleb nevus syndrome.

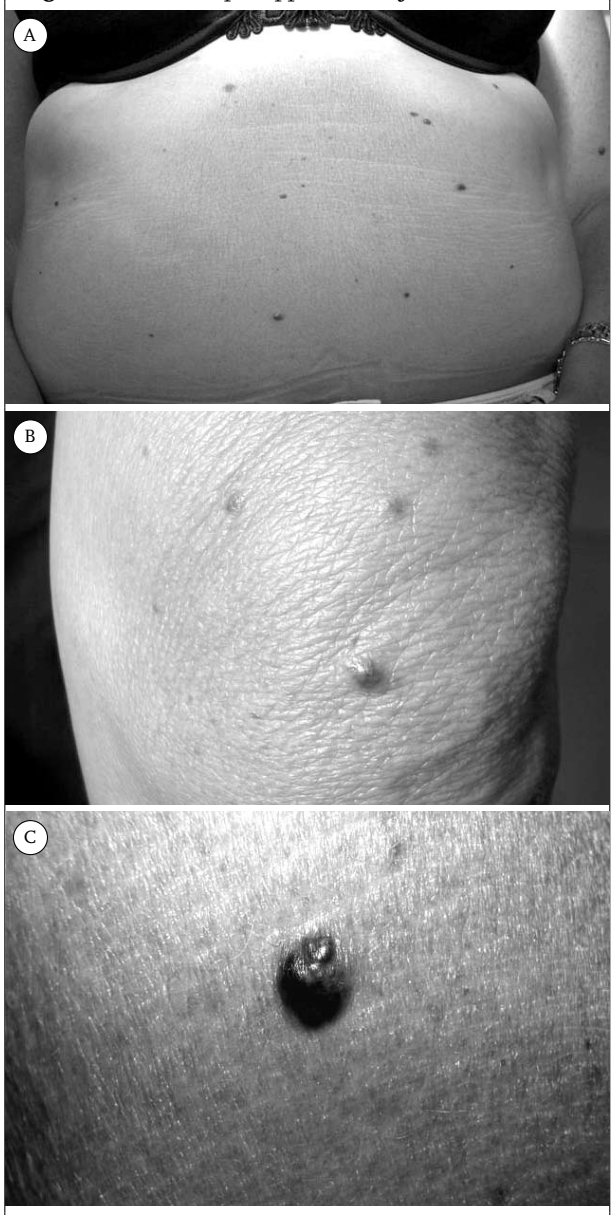
Because of the history of a possible pulmonary haemorrhage and the development of a hemiparesis, additional radiological examinations were performed. Computed tomography of the chest showed a large vascular malformation, while magnetic resonance imaging of the brain showed no malformations.

Treatment was initiated with a gluten-free diet and iron suppletion, after which she had an uneventful recovery, without any complaints.

DISCUSSION

The blue rubber bleb nevus syndrome (BRBNS) is a syndrome characterised by multiple vascular, mostly venous, blebs or nodules. Involved organ systems include the skin and visceral organs, most commonly the gastrointestinal tract. Less often, other organ systems are

Figure 1. *Macroscopic appearance of BRBNS lesions*



A. Localisations on the abdomen. B. Localisation on the knee. C. Detail of localisation on the knee.

Figure 2. *Endoscopic appearance of BRBNS lesions*

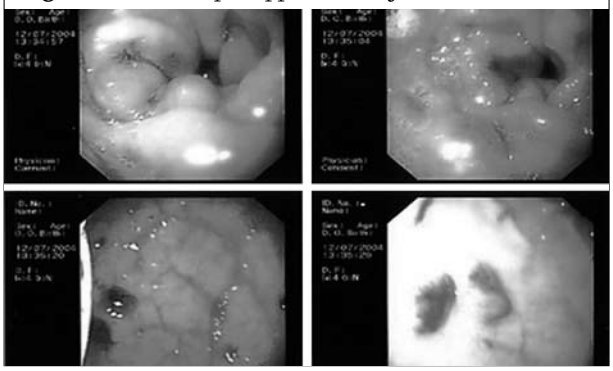
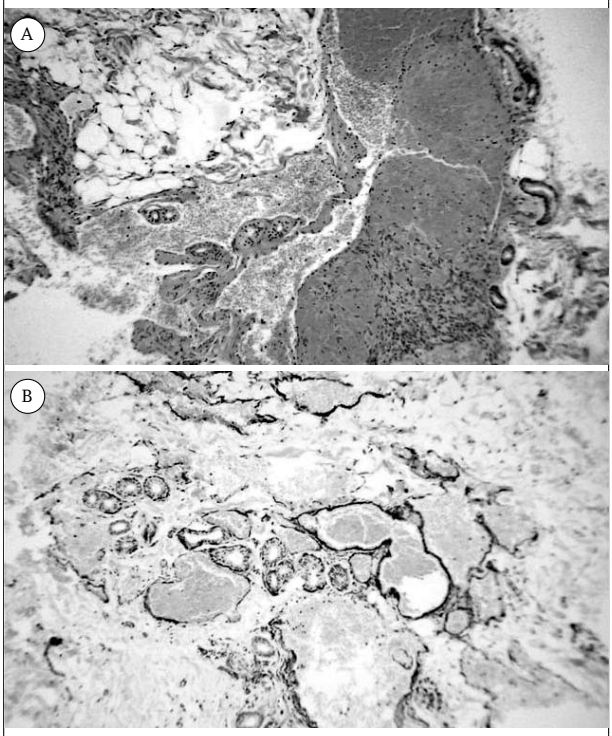


Figure 3. *Histopathological examination of BRBNS lesions*



A/B. Curled, ectatic vessels with single layer epithelium and connective tissue.

involved, including the central nervous system (CNS), musculoskeletal system, thyroid, parotid, eyes, oral cavity, spleen, lungs, kidney, liver, and bladder.[2-10] The syndrome was first described in 1860, when Gascoyen noticed an association between cavernous haemangiomas of the skin and similar lesions in the gastrointestinal tract.[11] In 1958, Bean, after further research, named this association the 'blue rubber bleb nevus syndrome'.[12] The BRBNS is a rare or under-recognised disorder: to date, fewer than 150 cases of BRBNS have been reported.

Cutaneous lesions are the main indicators for the diagnosis; however, they have a variable macroscopic appearance. The most classic cutaneous lesion consists of a nipple-like lesion, which is easily compressible and refills slowly on release of pressure. The lesion is mostly asymptomatic, but can be associated with pain and hyperhydrosis.[12] Histopathological examination of such lesions shows blood-filled ectatic vessels, lined by a single layer of endothelial cells, surrounded by thin connective tissue. The lesions show irregular cavernous spaces, located in both the deep dermis as well as subcutis, and often show smooth muscle fibres in vessel walls. In some cases, these vessels show an intimate relation with the sweat glands.[3,5] The diagnosis of BRNBS is initially based on the clinical cutaneous findings of characteristic lesions. However, other clinical conditions characterised by vascular abnormalities of the skin should be differentiated from BRBNS. Osler-Weber-Rendu disease (hereditary hemorrhagic telangiectasia) is a disease in which cutaneous lesions may look like the lesions in BRNBS. In addition, they are associated with similar lesions in the lungs and gut. However, the visceral and cutaneous lesions are typically smaller (2-5 mm) and more punctiform. The subungual lesions, nail-bed involvement, and spider and punctate telangiectases found in Osler-Weber-Rendu disease can help in distinguishing it from BRBNS. Maffucci's syndrome, also a disease with widespread cutaneous and visceral vascular lesions, is distinguishable from BRBNS by the bony abnormalities resulting from chondroplasia and defective ossification. Klippel-Trénaunay-Weber syndrome is identified by venous varicosities, soft tissue and bony hypertrophy, and cutaneous vascular malformations which are typically confined to one extremity. Other vascular disorders with cutaneous and visceral involvement are von Hippel-Lindau disease in which retinal and cerebellar angiomatosis occurs and the Sturge-Weber syndrome which is associated with meningeal angiomatosis. The unique cutaneous and extracutaneous findings can help distinguish these disorders from BRBNS.[2,3,13-18]

In BRBNS, the associated gastrointestinal venous malformations predominantly occur in the small intestine, but lesions may be found elsewhere in the digestive tract.[17,19-21] Gastrointestinal tract malformations are subject to frequent bleeding, potentially resulting in occult blood loss and iron-deficiency anaemia, as in the presented case.[4,5,13,19]

Most cases of BRBNS occur spontaneously; however, hereditary patterns with autosomal inheritance have also been reported in several case reports.[13,22] Some evidence suggests that the mutation for some cases of BRBNS may occur on chromosome 9p, because venous malformations were found to occur in association with an activation mutation in the receptor tyrosine kinase tie-2 also located at this same locus on chromosome 9p. However, tie-2 mutations have not yet been directly linked to BRBNS.[23-26] Complications of BRBNS include acute or, mostly, chronic blood loss, resulting in anaemia or pain in the affected organs. The most feared complication is CNS involvement resulting in CNS bleeding.[27,28] The prognosis depends on the extent of visceral organ involvement. Most patients have a normal lifespan.

Treatment options of cutaneous lesions include laser treatment, curettage or cryotherapy.[29-32] Surgical removal is usually not necessary. Depending on the presentation, extracutaneous lesions require symptomatic treatment, such as iron suppletion, endoscopic coagulation or surgery.[13,32-34]

Other conditions associated with cutaneous lesions as well as gastrointestinal blood loss include hereditary haemorrhagic teleangiectasia, in which epistaxis is often the initial manifestation. Pseudoxanthoma elasticum is a condition associated with yellow papules in intertriginious zones, angioid streaks in the eye, hypertension, premature atherosclerosis, uterine haemorrhage and vascular calcification, associated with upper or lower gastrointestinal bleeding. The Ehlers-Danlos syndrome type IV, an autosomal dominant inherited disease resulting in deficiency of type III collagen can be associated with upper gastrointestinal haemorrhage due to arterial rupture or intestinal perforation. The Gardner's syndrome (associated with epidermoid cysts, lipomas and desmoid tumours), the Peutz-Jeghers syndrome (associated with melanotic macules on mucosal surfaces) and Cowden's disease (multiple facial periorificial papules, cobblestoning of the oral mucosal surface, and acral keratotic papules) are associated with polyps in the gastrointestinal tract from which bleeding can occur. In addition, vasculitis syndromes can present with both cutaneous lesions and gastrointestinal haemorrhages. Scurvy, due to vitamin C deficiency, presents with perifollicular purpura and corkscrew hair and gingivitis and results in collagen degeneration in vasculature, which can lead to gastrointestinal blood loss. Inflammatory bowel syndromes such as ulcerative colitis and Crohn's disease can also be associated with cutaneous lesions such as erythema nodosum and pyoderma gangrenosum.[35]

In conclusion, our case demonstrates that combined loss of iron and malabsorption from the gastrointestinal tract can lead to severe iron deficiency. Early recognition of both diseases can result in early treatment. Patients can recover completely with iron suppletion and a gluten-free diet. Recognising typical BRBNS skin lesions would provide a potential diagnosis and could prevent unnecessary procedures or invasive surgery.

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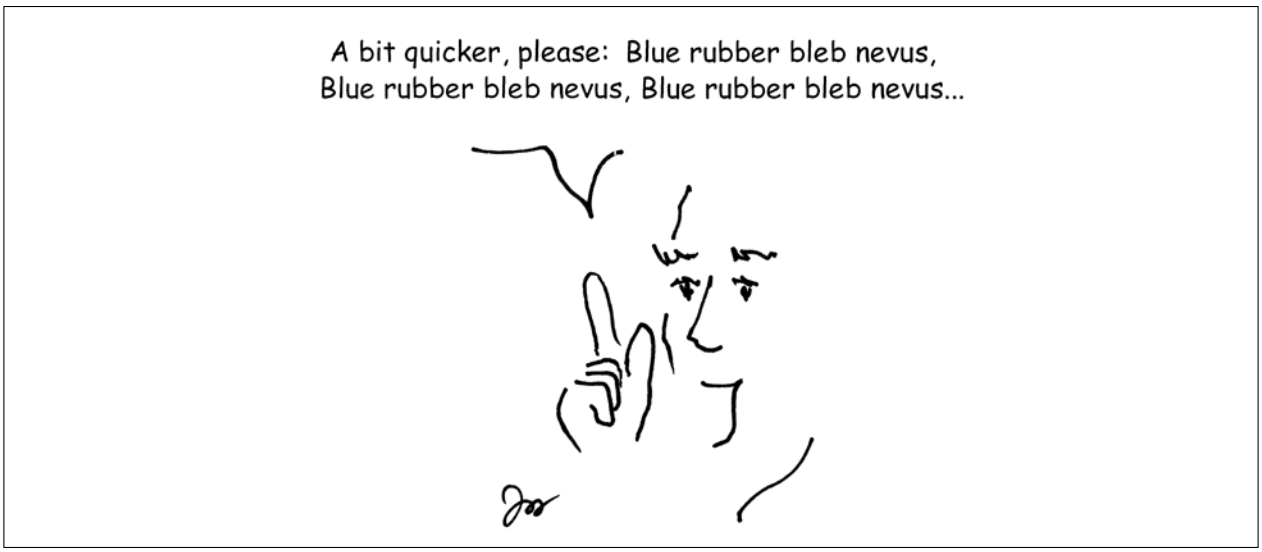

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