Quiz

Correct answer to the quiz. Check your diagnosis

Case report

Bean's syndrome (blue rubber bleb nevus syndrome – BRBNS) as a gastrointestinal bleeding – case report and review of the literature

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BRBNS is a rare syndrome of vascular malformations caused by the TEK mutation associated with numerous lesions of the skin and gastrointestinal tract. We present a case report of 41 year old man with severe anemia with recurrent bleedings. The detailed clinical, endoscopical and histopathological description is given as a wide range of differential diagnosis of vascular lesions based on pathophysiology and updated classification of vascular lesions. Clinicopathological diagnosis and treatment options of BRBNS are discussed.

Key words: Bean's syndrome (BRBNS), vascular malformation, TEK mutation, GLUT1, hemangioma.

Introduction

Bean's syndrome (blue rubber bleb nevus syndrome – BRBNS) is a rare morbidity associated with the venous malformations of vascular bed. In majority of cases BRBNS is caused by sporadic mutations of TEK gene which encode TIE2 – endothelial cell tyrosine kinase receptor of angiopoetins [1, 2, 3], few cases of germline mutations located on chromosome 9p has been also described [4, 5]. TEK mutation has also contributed to establishing BRBNS as a separate entity in international society for the study of vascular anomalies classification ISSVA [6]. The diagnosis of BRBNS is based on multidisciplinary approach with CT and MRI studies, endoscopic and histopathological examinations (supported by immunohistochemical stainings CD34, GLUT1, SMA, Ki67). Vascular malformations in BRBNS develop mostly in the skin and gastrointestinal tract and sporadically in CNS, liver, spleen, air tract, heart, urinal bladder and visceral spaces [7, 8, 9, 10]. BRBNS affects men and women equally with skin vascular lesion developing in early childhood followed by other localizations in adolescence. Up to 300 cases of BRBNS have been described in the literature thus far [4, 8, 11, 12].

Pathophysiology

The somatic double (cis) *TEK* (*TIE2*) gene mutations encoding angiopoetin receptor have been proved to cause BRBNS [2, 4]. The vascular bed of patients

with BRBNS is malformed with the presence of venous vascular malformations accompanied by vascular fistulas. The vessels are malformed and irregularly located and blood flow systems are dysregulated. The blood flow is turbulent, diameter's and resistance's dependent which cause thrombi formation and vascular autoamputations and ruptures. Significant bleedings mainly of gastrointestinal tract occur with secondary inflammation, ulceration and life threatening perforation. As a result of autoamputations or vascular malformation sclerotization neighboring vascular channels are overloaded and the blood stream is redirected to form new lesions. In addition some of new lesions are formed from mutated precursors cells mandating perpetuated nature of the diseases [2].

Case report

A 41-year-old man with recurrent gastrointestinal bleeding and secondary anemia requiring multiple blood transfusions, with protracted and increasing weakness. Physical examination revealed both flat

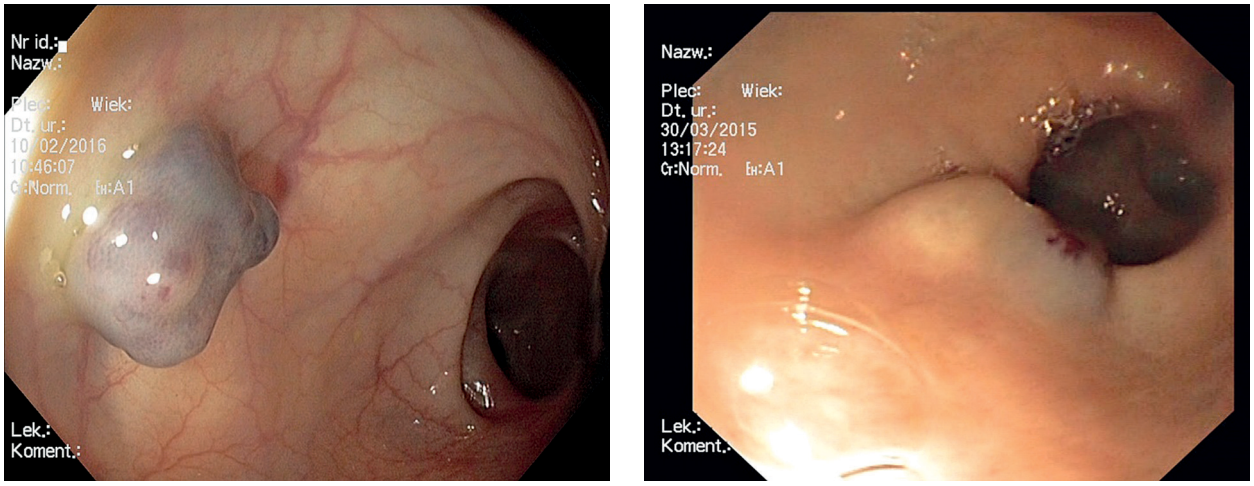

Fig. 1. Endoscopic examination: bluish polypoid submucosal lesions in large intestine and in the stomach

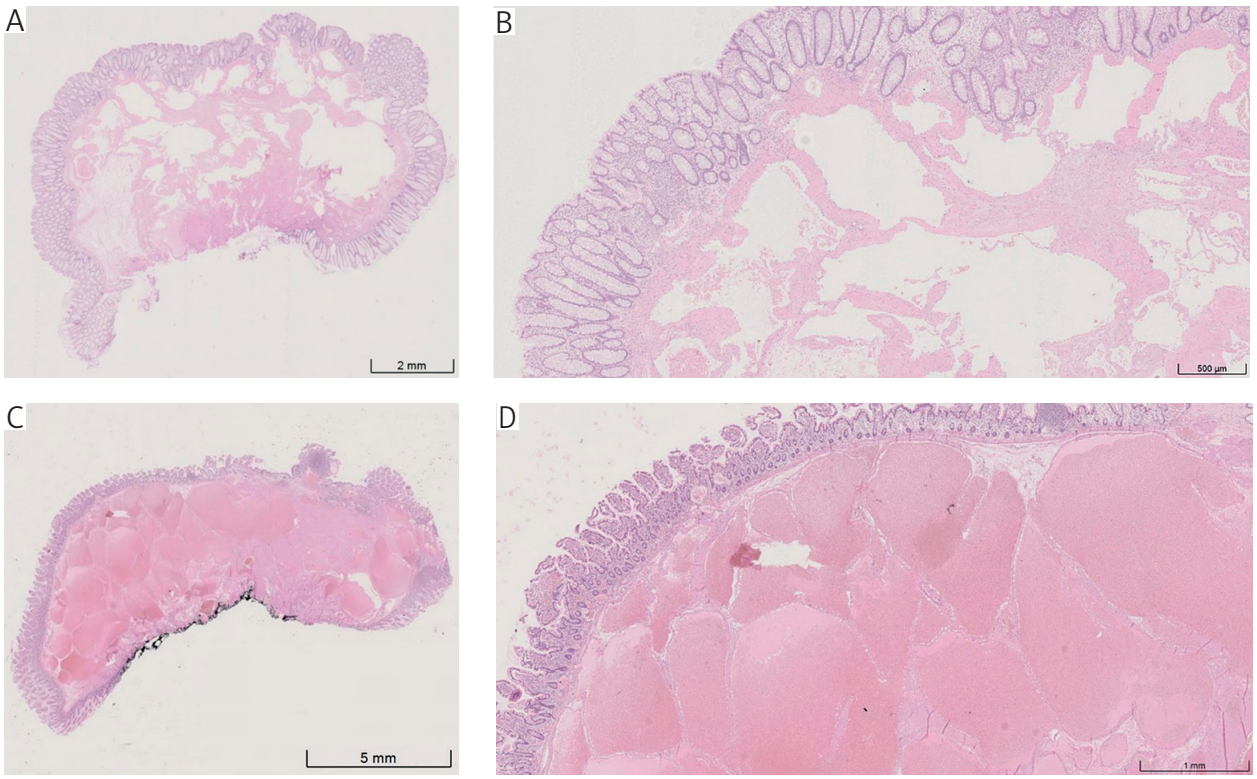

Fig. 2. A-D) Histopathological picture: wide vascular spaces in the submucosa lined with one layer of non-atypical endothelial cells. HE (see the text)

Table I. Modified after Wyrzykowski, Bukowski, Jaśkiewicz [9, 13]

HEMANGIOMA	VASCULAR MALFORMATION
CLINIC	
Appears in neonatal or early infant period – proliferation phase	Always present at birth
Grows faster then the child during first year	Grows proportionally with the child
Involution phase after 1 year of life	Never disappears
K:M 3-9:1 / incidence	K:M 1:1 / incidence
PATHOLOGY	
Proliferation phase: endothelial proliferation, numerous mastocytes	Flat, regular endothelial cells, normal numer of mastocytes
Involution phase: apoptosis, flattening of endothelial cells, dilated and less numerous vessels surrounded by fibroadiopse tissues	Regular endothelial cells renewal, dysplastic vascular channels, abnormal localization: veins, venules, capillaries, lymphatics

and protruded bluish, fading under pressure skin lesions with a slightly wrinkled surface in the perioral area, forearms and the left knee. In addition, post-surgical deformation of the right foot was found due to skin lesion excision in the childhood. In laboratory tests a low level of Hb 3.9 g/dl and iron deficiency were present. In the endoscopic examination of the gastrointestinal tract numerous, bluish submucosal lesions were found in esophagus, stomach (Fig. 1B), duodenum, small and large intestines (Fig. 1A). The size of the lesions was estimated from 0.2 mm to 4 cm. The patient was treated locally endoscopically, surgically and also received empiric chemotherapy without significant clinical improvement. The reemergence of new changes was observed. Histopathological biopsies revealed wide vascular spaces, thin-walled, lined with a single layer of endothelial cells with no atypia located within the submucosa of the gastrointestinal tract (Figs. 2 A-D, 3A). There were signs of fibrosis and hyalinosis in the surrounding tissue. The mucosa above the lesions revealed no significant pathological changes. Immunohistochemistry of vascular spaces lining: SMA+ CD34+, GLUT1– (Fig. 3B-D).

Discussion

BRBNS is a clinicopathological diagnosis [2, 10, 12, 14] and the morphological differential diagnosis include vascular malformations and vascular tumors (Table I). Unlike vascular malformations tumors generate hyperplasia of neoplastic cells. These cells differ metabolically from nonneoplastic lesions (Warburg effect) [15]. In the neoplastic cells overexpression of GLUT1 (erythrocyte type glucose transporter) is displayed in immunohistochemical stainings [16]. This reaction has both diagnostic and prognostic significance differentiating vascular malformations form vascular tumor mainly hemangiomas [16, 17].

BRBNS was initially described in 1860 by George Gascoyen [18] but the full description of the entity was introduced by William Bennet Bean in 1958 [19]. Vascular malformations in BRBNS are classically observed from the birth, particularly on hands and feet and gradually gastrointestinal tract lesions reveal. These lesions are in form of flat or protruded polyps growing slowly with acceleration in puberty which may indicate the association with hormonal factors. BRBNS is currently established based on the mutation in *TEK* (*TIE2*) gene and included in III category (simple vascular malformations named Blue rubber bleb naevus (Bean) syndrome VM TK (TIE2) of ISSVA classification for vascular anomalies (Amsterdam, Netherlands 2018) [20].

BRBNS is a phenotypic variant of *TEK* (*TIE2*) mutations and should be differentiated from other vascular malformations including multiple cutaneous and mucosal venous malformations (VMCS), multifocal venous malformations (MVM) and sporadical venous malformation (VM). The aforementioned entities belong to the TEK mutation spectrum and cannot be diagnosed solely on histopathological picture. The final diagnosis depends on inheritance mode, localization of the lesion and their number and size [2, 21]. In order to determine the extension of vascular lesion radiological techniques (US, CT, MRI, echocardiography) and endoscopy are utilized also to exclude the bone and soft tissue lesion which are not characteristic for Bean syndrome.

Outside the scope of TEK mutated syndromes the differential diagnosis of BRBNS include: Osler Weber Rendu syndrome of arterio-venous malformations (AVM) in the mucosa of oral and nasal cavities and minute pinpoint cutaneous teleangiectasies [10, 21], Klippel-Trenaunay syndrome of capillary-venous vascular malformation connected with hypertrophy or hypotrophy of the limbs [10, 22, 23] and Maffucci syndrome of vascular venous malformations

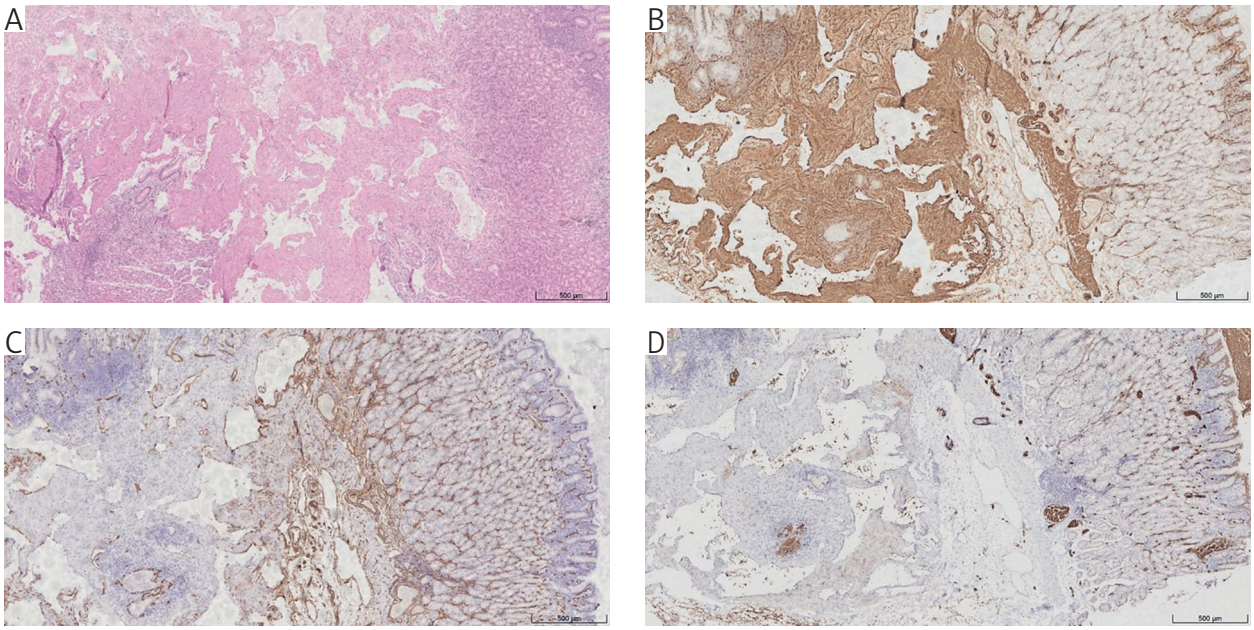

Fig. 3. Histopathological HE picture of widened vascular spaces in submucosa (A) and immunohistochemical positivity of SMA (B), CD34 (C) and GLUT1 (D) stainings (see the text)

and hemangiomas in gastrointestinal tract, bones, meninges accompanied by enchondromas or osteochondromas [10, 22, 24]. These patients are also at increased risk of developing cholangiocarcinomas, gliomas, acute leukemias and malignant transformation of vascular and chondral lesions [14, 25].

The treatment of patients with Bean syndrome has to be individualized based on severity of symptoms. In case of sporadic gastrointestinal bleedings iron supplementation and blood transfusions are usually sufficient. In case of severe bleeding the surgical or endoscopical procedure must be considered [10]. Different modes of BRBNS therapy has have been described in the literature with corticosteroids, interferon and propranolol, somatostatin analogues (octreotide) and sirolimus (rapamycin) [4, 9, 12, 26]. Sirolimus was proved to decrease gastrointestinal lesions, severe bleedings episodes and to increase the intervals between blood transfusions which all improve patients quality of life [3, 12].

The authors declare no conflict of interest.

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