BLUE RUBBER BLEB NEVUS SYNDROME (BRBNS)

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Introduction

Blue rubber bleb nevus syndrome (BRBNS) is a rare congenital disorder (OMIM # 112200) characterized by multifocal venous malformations mainly of the skin, soft tissue and gastrointestinal tract which may occur however in any tissue including the nervous system (Enjolras and Mulliken 1997, Fretzin and Potter 1965, Moodley and Ramdial 1993, Mulliken and Glowacki 1982, Munkvad 1983, Nahm et al. 2004, Paules et al. 1993).

BRBNS is characterised by distinctive cutaneous lesions, nocturnal pain and regional hyperhidrosis. Bleeding of the gastrointestinal tract is an important, and often fatal, complication but lesions of the brain and spinal cord occur (Andersen 2004, Deng et al. 2008, Edelstein et al. 2005, Garen and Sahn 1994, Shannon and Auld 2005, Wong et al. 1994).

Most BRBNS are sporadic and do not harbour mutations in the receptor tyrosine kinase/TEK-TIE2 (on chromosome 9p21) like in the so-called "*venous malformation multiple cutaneous and mucosal*" (VMCM) (OMIM # 600195) (Boon et al. 1994, Gallione et al. 1995, Tille and Pepper 2004). Until now there is no clear clinical-genetic differentiation between BRBNS and VMCM.

Historical background and eponyms

In 1860 Gascoyen probably reported the first case of an association of cutaneous and intestinal lesions with gastrointestinal bleeding in a 44-year-old man with anaemia and numerous cavernous hemangiomas of the skin. Gascoyen or Gaskoyen, referred to by one author, is probably the English dermatologist George Gaskoin (1818?–1887).

Almost a century later, in 1958, the hepatologist William Bean described a condition with similar findings in two individuals and reviewed the features of six others; he also coined the term "*blue rubber bleb nevus syndrome*" (Andersen 2004, Bean 1958).

William Bennett Bean was born in the Philippine Islands, but not long after the family moved to New Orleans and a few years later to Charlottesville, Virginia. Following graduation from medical school in Virginia, he interned on the Osler Service at Johns Hopkins and the following year he moved to Boston. Dr. Bean began his clinical career at the University of Cincinnati College of Medicine (1936–1946) and at Cincinnati General Hospital (1941–1948). In 1948 he became professor of medicine and head of internal medicine at the University of Iowa College of Medicine. In 1974, he was appointed Director, Institute for Medical Humanities and Professor of Internal Medicine at the University of Texas Medical Branch, Galveston. In 1980, he retired from the Institute and returned to Iowa City. Between 1937 and 1974, Bean published over 600 works in such diverse fields as nutrition, respiratory disease, myocardial infarction, climatology, arterial "spiders," slum eradication and housing, liver disease, William Osler, Walter Reed, and the history of medicine (History of Medicine 2006, Who named it? 2006).

The inaccurate use of the term "*hemangioma*" for the malformations of BRBNS in general reflected the traditional use of the cavernous hemangiomas when referring to venous malformations. Mulliken and Glowacki (1982) helped to clarify

our thinking regarding vascular anomalies by proposing that these would be categorized as either hemangiomas or malformations on the basis of their cellular features in relation to their clinical appearance and natural history. A modification of this classification system was accepted by the International Society for the Study of Vascular Anomalies (ISSVA) (Enjolras and Mulliken 1997). They proposed that *vascular anomalies* (VA) can be classified as *tumours* or *malformations* of diverse vascular origin. *Vascular malformations* (VM) result from errors of vascular morphogenesis and are named by their predominant vessel type: arterial, venous, capillary, lymphatic or different combinations of each of them. Venous malformations, often improperly termed "cavernous hemangiomas", are the most frequent vascular abnormality. They are present at birth, thought often they often become apparent afterward. In BRBN, the vascular lesions represent a peculiar type of venous malformations (Tille and Pepper 2004).

BRBNS is also known as Bean's dollar bill skin; Bean syndrome; Blaues Gummiblasen-Syndrom (in Germany); cutaneous-intestinal cavernous hemangioma; and naevus caoutchouc-bleu (in France).

Incidence and prevalence

The syndrome is quite rare with approximately 200 cases reported in the world's literature but its precise incidence is unknown (Andersen 2004, Cherpelis and Fenske 2006, Edelstein et al. 2005). BRBNS has been reported in persons of all races, although whites appear to be most frequently affected. Males and females are equally affected.

Clinical manifestations

Skin manifestations

BRBNS is characterized by highly distinctive cutaneous lesions, as multiple, protuberant, dark blue, compressible blebs, a few millimetres to several centimetres in diameter and varied in hues and shapes. They usually do not bleed and can be classified into 3 types (Bean 1958):

- Type 1 is a large disfiguring, cavernous lesion that may compress and/or obstruct vital structures (Fig. 1).
- Type 2 are the most classic cutaneous lesions: these are rubbery raised bluish-to-black lesions, soft and easily compressible, leaving an empty sack after pressure that refills slowly they are considered nipple like lesions (Fig. 2). Sometimes hyperhidrosis is seen on their overlying skin (Moodley and Ramdial 1993, Tunkvad 1983).
- Type 3 is an irregular blue-black macule or papule that rarely may blanch when pressure is applied (Fig. 3).

Skin lesions may be seen on any cutaneous surface, but the trunk, limbs and face are the most frequently involved sites and may appear immediately after birth, in infancy, or even later beyond midlife (Cherpelis and Fenske 2006, Mejia-Rodriguez et al. 2008). The number and size of lesions can increase with age (Fine et al. 1961, Fretzin and Potter 1965, Moodley and Ramdial 1993, Nahm et al. 2004, Romao et al. 1999). They usually do not bleed and are rarely painful. No malignant change of skin lesions has been reported so far (Moodley and Ramdial 1993, Munkvad 1983).

Systemic involvement

Gastrointestinal tract

In addition to the cutaneous involvement, vascular lesions are usually found in the gastrointestinal tract, anywhere from the oral to the anal mucosa, but predominantly in the small bowel (McKinlay et al. 1998, Moodley and Ramdial 1993, Paules et al. 1993) (Fig. 4). The most common mode of presentation of BRBNS is gastrointestinal bleeding. Lesions are typically discrete mucosal nodules with a central bluish nipple, although they may be flat, macular or polyploid. They vary in size and number but there is no correlation with extent of cutaneous involvement (Gallo and McClave 1992, Nahm et al. 2004, Sandhu et al. 1987).

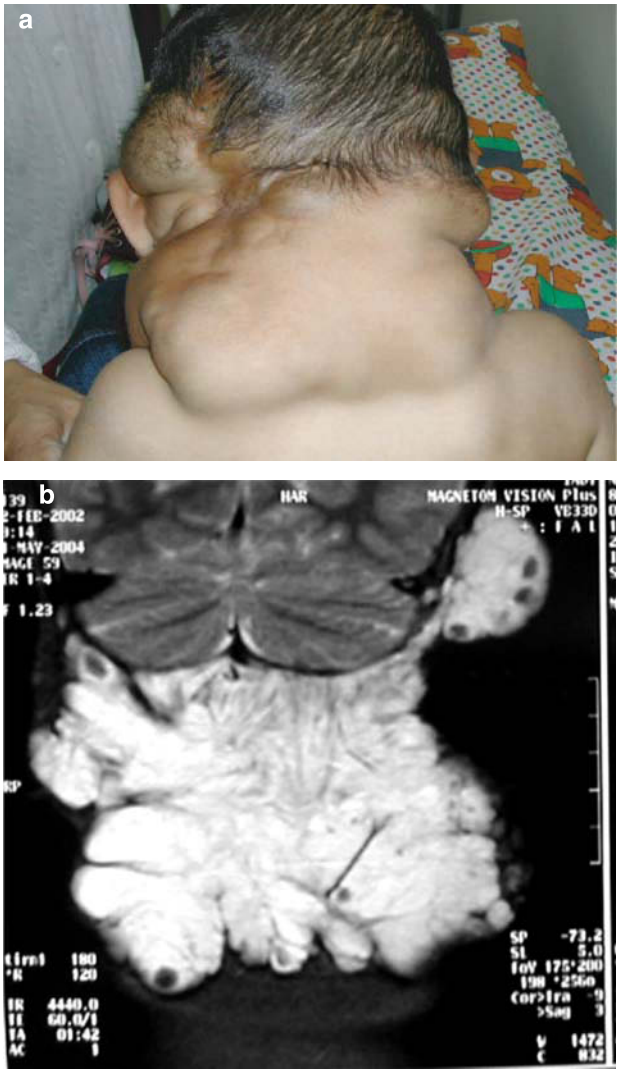

Fig. 1. (**a**) A large, complex, disfiguring, cavernous lesion of the neck and upper shoulders compressing vital structures in a child with BRBNS; (**b**) corenal T2-weighted MR image shows marked increased signal intensity of the venous component of a large tumour in the posterior fossa.

Gastrointestinal lesions may appear from infancy to adulthood, they are generally multiple and tend to bleed easily, often leading to iron deficiency anaemia, due to occult blood loss or acute haemorrhage, requiring iron supplementation or blood transfusions (Baker et al. 1971, Berlyne and Berlyne 1960, McIntosh and Harris 1970, Sandhu et al. 1987). Acute bleeding, presenting as hematemesis, melena or rectal bleeding may occur. Hemorrhage is occasionally massive and life-threatening requiring blood transfusion or surgical intervention without any delay (Baker et al. 1971, Fishman et al. 2005, Romao et al. 1999, Shahed et al. 1990). Occasionally they cause other types of complications such as intussusception, volvulus, intestinal infarction, internal hemorrhage or rectal prolapse (Lee et al. 2008). Therefore, in a patient with BRBNS the presence of abdominal pain or signs of intestinal obstruction should always be evaluated carefully (Beluffi et al. 2004, Browne et al. 1983, Moodley and Ramdial 1993, Nahm et al. 2004).

Other organs

Many other organs may be involved: liver, spleen, heart, lung, pleura, peritoneum, kidney, thyroid, pararotid, bladder, oronasopharyns, penis, vulva, cervix, eyes, skeletal muscle, bone and brain (Carvalho et al. 2003, Gascoyen 1860, Lichtig et al. 1971, Malhotra et al. 2008, Moodley and Ramdial 1993, Munkvad 1983, Paules et al. 1993, Radke et al. 1993, Starr et al. 2005, Tanaka et al. 2007) (Figs. 5 and 6). In addition to skin and gastrointestinal tract lesions orthopaedic abnormalities are often present. Skeletal anomalies may arise from pressure of adjacent venous malformations into bone structures (Fig. 6). Hypertrophy may occur as a result of hypervascularity. Skeletal bowing as well as pathologic fractures have also been reported (Manoury et al. 1990, Mckinlay et al. 1998, Tzoufi et al. 2007).

Sakurane et al. (1967) described cavernous hemangiomas characteristic of BRBNS over the entire surface of the body and in the mucosa of the oropharynx, oesophagus, distal ileum and anus. In addition the patient had multiple enchondromatosis (Sakurane et al. 1967).

Central nervous system

Although central nervous system involvement is rarely described, there has been a number of reports of variable cerebral vascular and arteriovenous malformations in BRBNS (Fig. 1b) including dural arteriovenous fistula (Carvalho et al. 2003) vascular malformations

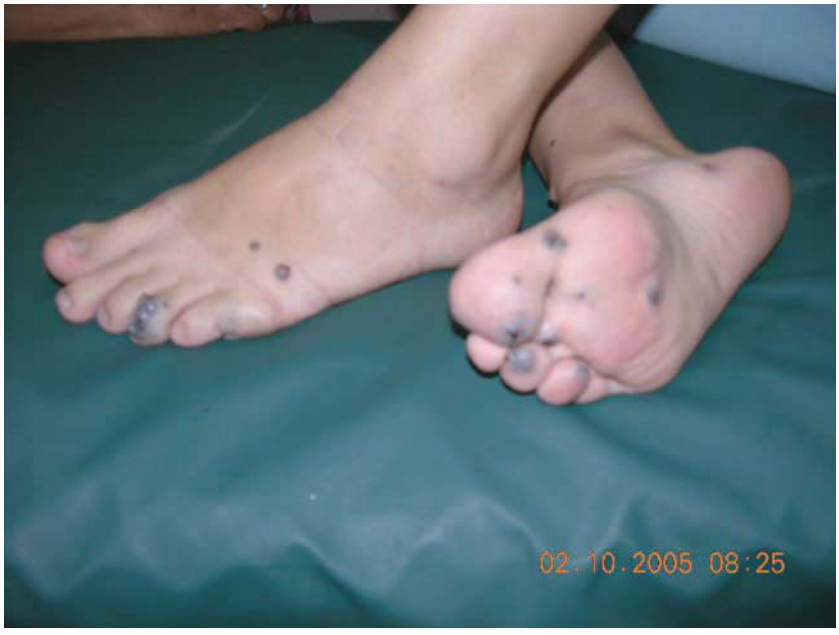

Fig. 2. Rubbery raised bluish-to black lesions, soft and easily compressible, nipple like lesions in the feet of a man with BRBNS.

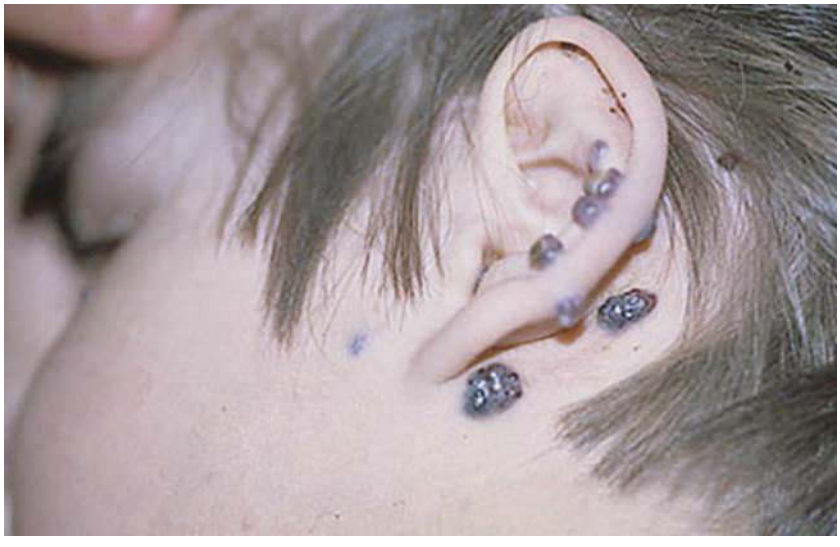

Fig. 3. Irregular blue-black papules in the auricular and sub auricular region in a child with BRBNS.

(Gil-Nunez et al. 1983, Hashimoto et al. 1989, Jaffe 1929, Kunishige et al. 1997, Satya-Murti et al. 1986, Wood et al. 1957), developmental venous anomalies including vein of Galen malformation (Waybright et al. 1978) and sinus periocranii (Gabikian et al. 2003) giant venous angioma (Sherry et al. 1984), vertebral hemangiomas (Garen and Sahn 1994), mixed vascular malformations (Rice and Fischer 1996, Rosenblum et al. 1978) and multiple cerebral and cerebellar vascular malformations with foci of haemorrhage in both occipital lobes (Shannon et al. 2005, Tzoufi et al. 2007).

Bleeding can occur in any affected site leading to different clinical pictures. If sufficiently severe, anaemia can cause additional neurological symptoms (Andersen 2004). Focal seizures seem to be the most common initial neurological problem (Bean 1958, Waybright et al. 1978, Kim 2000). Neurological

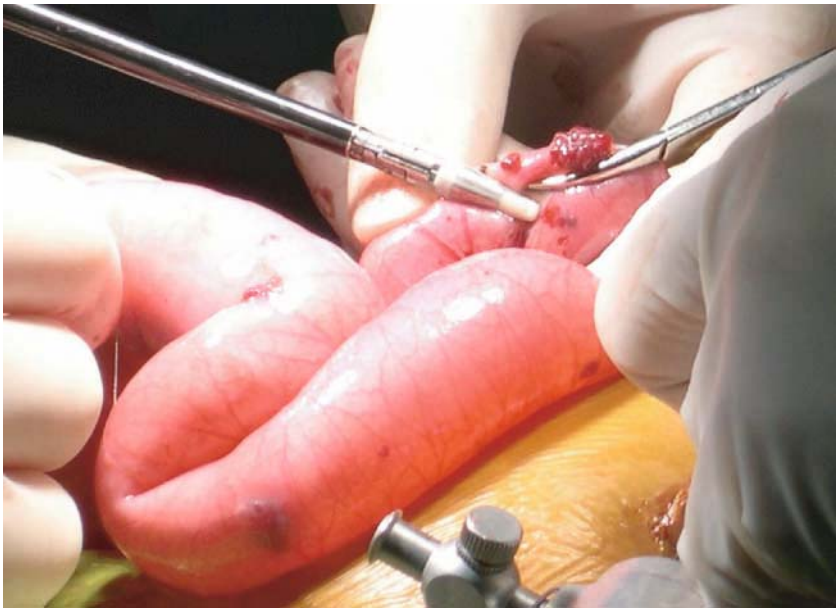

Fig. 4. Evidence of blue bleb lesions in a segment of gastrointestinal tract shown during resection of the involved segment of gut.

signs included so far weakness, ataxia, ophthalmoplegia, visual field defects and cortical blindness (Kim 2000, Satya-Murti et al. 1986, Shannon and Auld 2005, Wong et al. 1994). If the lesion is around the spinal cord, medullar compression requiring emergency surgery can occur (Garen and Sahn 1994, Wong et al. 1994) or progressive leg pain and weakness after minor back injury can ensue (Garen and Sahn 1994). Satya-Murti et al. (1986) described a young adult with central nervous system involvement: the patient presented with a slowly progressive ataxia and brain stem signs including palatal myoclonus. A large posterior fossa, and multiple smaller hemispheric vascular lesions were noted. Waybright et al. (1978) described another patient with severe headaches who had a thrombosed Galen's vein malformation.

Imaging

Radiographic images may be useful in suspected bone or joint involvement to detect fractures, bony overgrowth, and articular derangement (Cherpelis and Fenske 2006). Radiographic contrast techniques may detect gastrointestinal lesions, but endoscopy is considered to be superior. Upper gastrointestinal endoscopy is more sensitive than an upper gastrointestinal series and colonscopy more useful than a barium enema. Endoscopy also provides the opportunity to treat and diagnose the lesion(s).

Multifocal intracranial calcifications (most often located in the caudate nucleus and posterior fossa) (Edelstein et al. 2005) are sometimes evident with computed cranial tomography (CT) (Waybright et al. 1978). These calcifications may stem from thrombosis within the vascular lesion (Andersen 2004). Contrast enhancing lobulated intraconal orbital lesions consistent with hemangiomas are demonstrated by computed tomography. Larger lesions of similar nature may be seen within the soft tissues of the neck, in association with partial thromboses and hyperdense phlebolyts (Edelstein et al. 2005).

CT scans show the extent of the lesions which are hypodense or heterogeneous before contrast and enhances peripherally and slowly after injection of contrast. Magnetic resonance imaging (MRI) is an excellent technique for defining the extent of the lesions and their relationship to adjacent structures. On T1-weighted images, venous malformations are hypointense or jointense compared to the muscle. They may present with an heterogeneous on intermediate signal secondary to

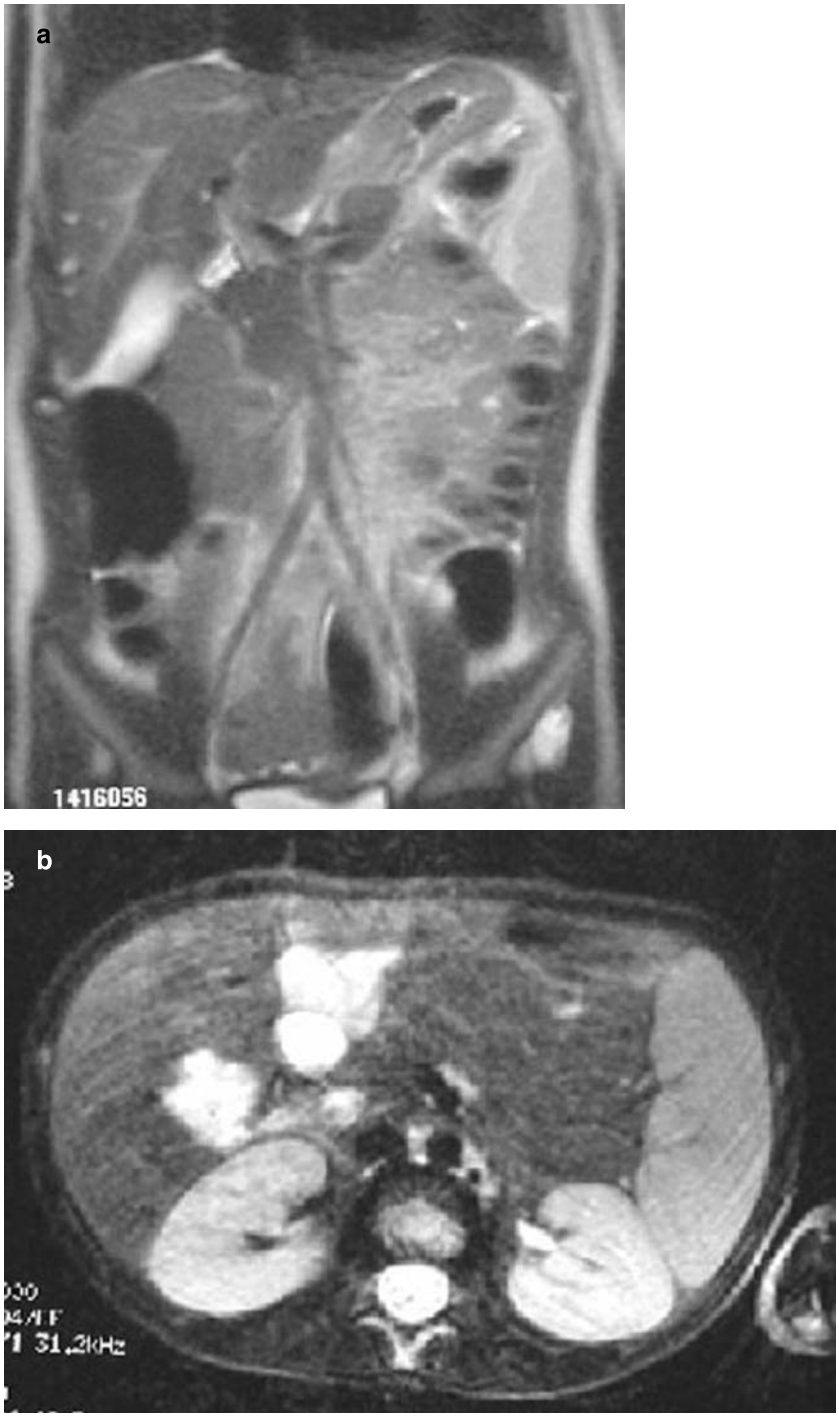

Fig. 5. MR (**a**) and CT (**b**) appearance of multiple cavernous lesions in the internal organs.

thrombosis or haemorrhage. Absence of flow voids is mandatory for the diagnosis of venous malformations.

MRI and/or MR angiography is a useful tool for detecting extracutaneous lesions and fro screening of asymptomatic members. Patients with brain involve-

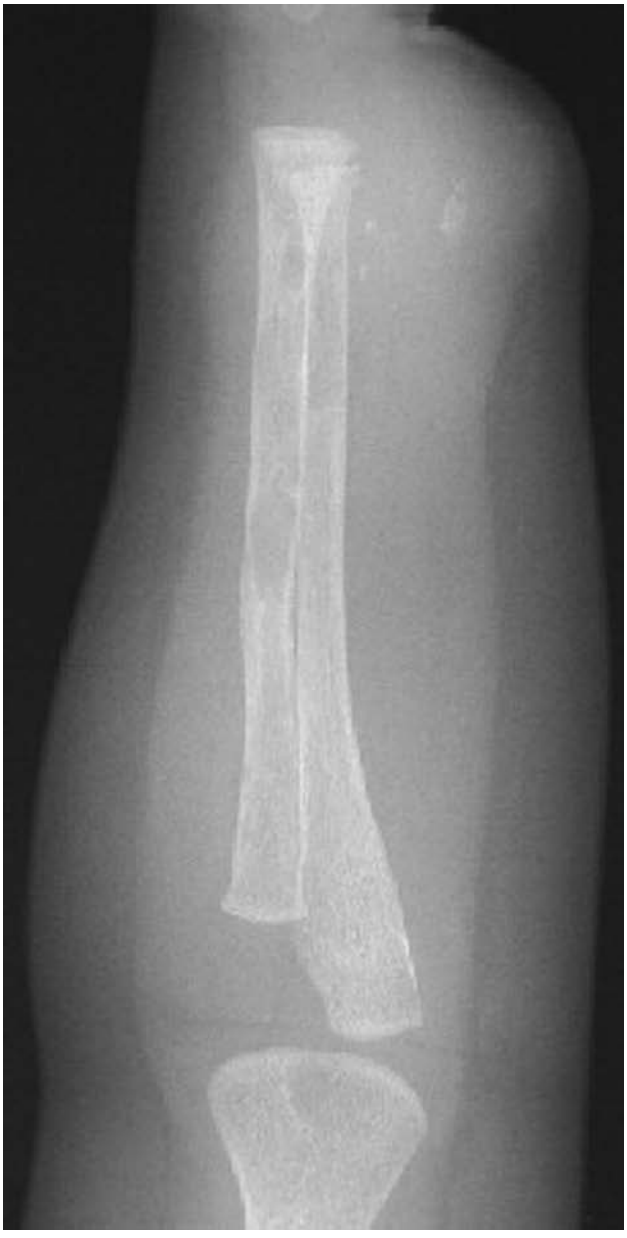

Fig. 6. X-ray demonstration of bone involvement.

ment show at MRI one or more lesions (Kim 2000). Flow voids and areas of moderate to marked contrast enhancement within the cerebellum, caudate nucleus, and cerebral cortex indicate vascular lesions of diverse size. These correlate angiographically with vascular malformations but are not true arterovenous malformations, since they show no definite arteriovenous shunting (Edelstein et al. 2005). Larger lesions may be apparent in the late phases of cerebral angiography (Satya-Murti et al. 1986). MRI and MR angiography also display anomalous venous sinuses, thromboses of sinuses, and adjacent cerebral atrophy, presumably related to altered flow dynamics (Edelstein et al. 2005).

The vertebral bodies may show stippled "honey comb" lesions characteristic of vascular lesions and any associated epidural malformation within the spinal canal, as well as any concurrent epidural haematoma or spinal block (Edelstein et al. 2005).

Natural history

The natural history and overall prognosis of BRBNS is unknown. However, systemic complications begin to appear after the age of 10–20 years (Oranje 1986), and sudden massive gastrointestinal hemorrhage remains the most frequent cause of death (Edelstein et al. 2005). Affected patients usually present to the dermatologist because of cosmetic concerns. Physical complaints or symptoms vary depending on the organ system involved. Venous malformations that occur intra or extra-articularly may lead to pain, decrease joint range of motion and occasionally deformity. Soft tissue involvement in or near a muscle bulk may adversely affect the surrounding or adjacent muscle function (Maunoury et al. 1990, Mckinlay et al. 1998).

Patients may present with blindness due to cerebral or cerebellar vascular lesions that may hemorrhage into the occipital lobes.

BRBNS has been also associated with several tumours: meduloblastoma, chronic lymphocytic leukaemia, hypernephroma, and squamous cell carcinoma (Hoffman et al. 1978, Lichtig et al. 1971, Rice and Fischer 1996).

Extensive venous malformations, mainly if located in the trunk or a limb, was associated with a lifelong, low-grade localized intravascular coagulopathy, characterized by low fibrinogen and high D-dimer levels. This could evolve to disseminated intravascular coagulopathy following trauma, surgery, or sclerotherapy (Hofhuis et al. 1990, Lichtig et al. 1971).

Pathology

Histologically, the skin lesions consist of large, irregularly dilated, mature endothelial-lined channels with insufficient (or too thin) layer of connective tissue and surrounding smooth muscle. This abnormal mural structure allows the lesions to expand slowly over time. The first type of histopathology change has been observed in the superficial dermis, whereas in the deep dermis or in subcutaneous lesions, the second an third type of pathologic are generally described (Fine et al. 1961, Fretzin and Potter 1965, Rice and Fischer 1996, Walshe et al. 1966).

Little information is available about the brain pathology of BRBNS, but the brain lesions grossly and histologically resemble those of the skin (Waybright et al. 1978).

Pathogenesis and molecular genetics

Although BRBNS usually occur sporadically, Berlyne and Berlyne (1960) demonstrated transmission through 5 generations; Walshe et al. (1966) reported on two families with affected persons in 3 and 5 successive generations; Munkvad (1983) reported a family with 7 affected persons (without visceral involvement) in 3 generations, including father-to-son transmission. Other families with autosomal dominant transmission have been reported by Moodley and Ramdial (1993) as well as families with only male to male transmission (Talbot and Wyatt 1970).

Knoell et al. (1998) described familial multiple blue nevi, histologically shown to be of the Jofassohn-Tieche type, occurring in a dominant inheritance pattern over 4 generations, without associated abnormalities (OMIM # 603670) (OMIM 2006). Additional families with several bluen nevi of the cellular type have been described by Blackford and Roberts (1991). Either families however appear to be distinct from the BRBNS (OMIM 2006).

Gallione et al. (1995) first postulated that BRBNS might be likely a variety of the so-called "*venous malformation multiple cutaneous and mucosal*" (VMCM), a phenotype first reported by Boon et al. (1994) in 15 members of 3 generations who had small cutaneous venous malformations associated to "slow-flow" venous malformations of soft tissues and bleeding of the gastrointestinal tract (OMIM # 600195) (OMIM 2006). The lesions in VMCM may present at birth but usually appear by puberty. Notably, histopathology examination of the affected blood vessels in this phenotype shows the same features as in BRBNS. Genetic linkage studies have implicated a region on chromosome 9p21 in two unrelated VMCM families (Boon et al. 1994, Gallione et al. 1995, Vikkula et al. 1996). The disease gene was subsequently identified as the receptor tyrosine kinase/TEK (TIE2) (Calvert et al. 1999, Gallione et al. 1995), a controller of endothelial cell assembling and remodelling which organises the vascular network hierarchically into large and small vessels and recruits perivascular cells that are necessary to stabilise vessel structures (Tille and Pepper 2004). It is important to note that some VMCM families do not show linkage to the TIE2 locus (Calvert et al. 1999) suggesting the existence of additional loci for inherited venous malformations (Tille and Pepper 2004). As we expressed earlier, the majority of true BRBNS are sporadic and do not carry the TIE2 mutation like in VMCM. Many reports in the literature of familial BRBNS are actually cases of glomangiomas and there is a potential for confusion because of the clinical similarities between both disorders (Lu et al. 2005). Autosomal dominant inheritance has also been reported in both diseases, although familial cases of multiple glomangiomas occur more frequently. For this reason, it is very important to perform a biopsy of all cutaneous lesions.

Diagnosis

Diagnosis of BRBNS is initially based on clinical-cutaneous findings of the characteristic skin lesions, and confirm by imaging studies and endoscopic finding of the gastrointestinal lesions (Arguedas and Wilcox 1999, Baker et al. 1971, De Bona et al. 2005, Fish et al. 2004, Gallo and McClave 1992, Radke et al. 1993, Rosenblum et al. 1978).

Anaemia due to gastrointestinal bleeding is frequent and it is important to consider this syndrome in

cases of unexplained anaemia to search for the characteristic skin lesions (Baker et al. 1971, Bean 1958, Berlyne and Berlyne 1960, Fretzin and Potter 1965).

Consumption coagulopathy associated with thrombosis is a different type of clinical presentation (Gonzalez et al. 2001, Hofhuis et al. 1990)

Careful examination of the patient, searching for other sites of involvement is helpful in supporting the diagnosis. Computed tomography (CT) and magnetic resonance imaging (MRI) also may be useful, non invasive methods, in evaluating internal lesions in these patients (Garen and Sahn 1994, Gascoyen 1860, Satya-Murti et al. 1986, Shannon and Auld 2005, Starr et al. 2005, Waybright et al. 1978).

For the gastrointestinal compromise, diagnosis can be established by upper endoscopies and colonoscopies if lesions involved oesophagus, stomach, duodenum and colon. For lesions in the small bowel several investigations can be employed: capsule endoscopies, intraoperative enteroscopy and push-enteroscopy (Fig. 4). Capsule endoscopy has recently been proposed as a new non-invasive endoscopic procedure for evaluating the small bowel (Arguedas and Wilcox 1999, Badran et al. 2007, De Bona et al. 2005, Fish et al. 2004, Kopacova et al. 2007, Maunoury et al. 1990, Radke et al. 1993).

For another unusual type of presentations such as acute abdominal pain due to intussusception, cortical blindness, spinal cord compression, other CNS symptoms, as well as, suffocation due to airway compromise, the syndrome should be suspected if the characteristic skin lesions are present or if there is an antecedent of gastrointestinal bleeding (Beluffi et al. 2004, Browne et al. 1983, Carvalho et al. 2003, Garen and Sahn 1994, Gascoyen 1860, Rice and Fischer 1996, Rosenblum et al. 1978, Shannon and Auld 2005, Starr et al. 2005, Waybright et al. 1978).

Differential diagnosis

BRBN must be differentiate from hereditary hemorrhagic telangiectasia (Rendu Osler Weber Syndrome), where the skin lesions are red and pinpoint with noticeable telangiectasia (Moodley and Ramdial 1993).

Multiple glomangiomas have been confused with the lesions of BRBN, they never have gastrointestinal involvement (Lu et al. 2005).

Maffuci syndrome has widespread vascular low flow cutaneous and visceral involvement but its lesions are distinguishable by the bony abnormalities resulting from dyschondroplasia and defective ossification (Shepherd et al. 2005).

The dermal nodule of BRBN should be distinguished from a distinct type of vascular malformation named “venous nevus” or “nevus venous” (Zeitz et al. 2008) which consists in an extratruncal venous malformation of the skin or the neighbouring mucosa arranged in segmental patterns.

Treatment

The most important clinical problem for these patients is the management of acute or chronic bleeding from the multiple gastrointestinal venous malformations. A conservative approach should be instituted whenever the clinical features and the bleeding episodes are mild. Another point in the surveillance and follow-up of BRBNS patients is iron deficiency anaemia due to acute of chronic gastrointestinal bleeding as was seen in almost all of the patients. Continuous oral iron are usually adequate to the management of most of the cases. Resection of the affected intestinal segment is recommended when there is significant bleeding and the lesions are confined to one segment of the gastrointestinal tract. Gastrointestinal lesions can be also treated by sclerosing agents (Baker et al. 1971, Berlyne and Berlyne 1960, Fishman et al. 2005, McKinlay et al. 1998, Moodley and Ramdial 1993, Munkvad 1983, Nahm et al. 2004, Paules et al. 1993).

Cutaneous lesions are seldom treated unless they are cosmetically or functionally troublesome. Recurrences or hypertrophic scars often result from surgical excision (Paules et al. 1993). Treatment of the skin lesions with CO_2 laser, whereas combined with oral steroids or not has been reported (Dieckermann et al. 1994, Fine et al. 1961).

A variety of therapeutic agents have been used for the management of GI bleeding in BRBNS including antiangiogenic agents such as corticosteroids

and interferon alpha and endoscopic approaches (Boente et al. 1999, De Bona et al. 2005, Maunoury et al. 1990, Shahed et al. 1990).

Thrombocytopenia and chronic consumption coagulopathy have also seen described in this syndrome. Transfusions may occasionally be required (Hofhuis et al. 1990).

Octreotide a somatostatin analogue has been used to treat acute and chronic upper GI bleeding in adults and children (Bowers et al. 2000, Zellos and Schwarz 2000). Its role in long term treatment o chronic GI bleeding is unclear but is safe and affective for the management of chronic GI blood loss as a result of a variety of causes (Gonzalez et al. 2001, Siafakas et al. 1998, Zellos and Schwarz 2000).

The management of the GI lesions depends on the extent of involvement and the severity of GI bleeding. If the bleeding is significant and the vascular lesions are confined to a segment of gastrointestinal tract, resection of the involved segment of gut is indicated (Fishman et al. 2005).

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