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Blue rubber bleb naevus syndrome

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Summary. An autopsy case of blue rubber bleb naevus syndrome (BRB-NS) is reported. There was the usual occurrence of cavernous haemangioma in the skin and intestine and cardiac involvement by a haemangiomatous lesion might have directly led to the patient's death. By light and electron microscopy, all the haemangiomatous lesions examined were cavernous with the exception of the cardiac tumour which was a mixed-vessel (capillary and cavernous) type of a haemangioma. These findings indicate that any vascular tumour-like lesions may occur in BRBNS. The principal combination of haemangiomas in the skin and intestine in BRBNS regardless of their type is the typical feature of this syndrome.

Key words: Blue rubber bleb naevus syndrome – Cavernous haemangioma – Capillary haemangioma

Introduction

The blue rubber bleb nevus syndrome (BRBNS) was first documented by Bean (1958) and is characterized by an association of cutaneous haemangiomas with gastrointestinal haemangiomas leading to iron deficiency anaemia from persistent melaena. The cutaneous haemangiomas are usually cavernous (Fretzin and Potter 1967) and the involvement of various internal organs has been demonstrated. McCauley et al. (1979) found more than 40 reported cases of BRBNS, however, the number of autopsy reports is still limited (Bean 1958; Rice and Fischer 1962; Lichtig et al. 1971; Waybright et al. 1978). The present report illustrates an autopsy case of BRBNS in which haemangiomas occurred in the unusual organs, and cardiac involvement might have led to the patient's death.

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Case report

A 63-year-old housewife was admitted to the Emergency Unit of Tokyo Medical College Hospital with the complaint of dyspnoea in January, 1981. She had suffered from chronic heart failure since her twenties. Blood pressure was 140/90 mmHg and cardiac enlargement was revealed by roentgenogram. An extrarenal tumour was detected incidentally in the left hypochondrial peritoneal cavity by pyelogram. Soy bean-sized bluish naevuslike lesions in the subcutis were found in the lower lip, oral cavity, limbs and back. Stool occult blood was repetitively positive during admission. A skin biopsy from upper arm indicated cavernous haemangioma, and BRBNS was diagnosed. She was discharged because of improvement of dyspnoea in April, 1981 and readmitted to the Department of Internal Medicine of the same hospital with the complaints of dys- and orthopnoea in March, 1985. Renal failure was distinct and she was under the nephrotic syndrome. These various symptoms were improved with beta-blocker and diuretics. She was discharged again in September, 1985. She was admitted three times to the same department with cardiac failure and anaemia in December, 1985. Atrial flutter was evident on ECG. Congestive heart failure became worse, and she died of cardiac failure on 10 January, 1986. The chief laboratory findings were: RBC $241 \times 10^4/mm^3$, haemoglobin 6.3 g/dl, WBC $4{,}500/mm^3$, platelet $185 \times 10^3/mm^3$, blood urea nitrogen 25.5 g/dl and creatinine 2.35 g/dl. Fasting blood sugar, serum total protein, serum bilirubin, GOT and GPT were within normal limits.

On external inspection after death, subcutaneous flat naevus-like lesions were seen in the lower corner of the mouth, the right shoulder, both left and right upper arms, right forearm, left hand and right upper thigh. These lesions were bluish purple and were eleven in all (0.5 to 3.0 cm diam.).

The heart (530 g) showed biventricular hypertrophy with dilatation. The myocardium at the subendocardial region of the ventricular wall beneath the anterior mitral valve cusp was replaced with grayish white rubbery tumour that was demarcated for $2 \times 1 \times 1$ cm from the surrounding myocardium (Fig. 1a). The liver (690 g) was congestive. Grayish white rubbery nodule (1 cm diam.) was found in the centre of the right lobe. Around 1.5 cm from that nodule, there was a blood pool

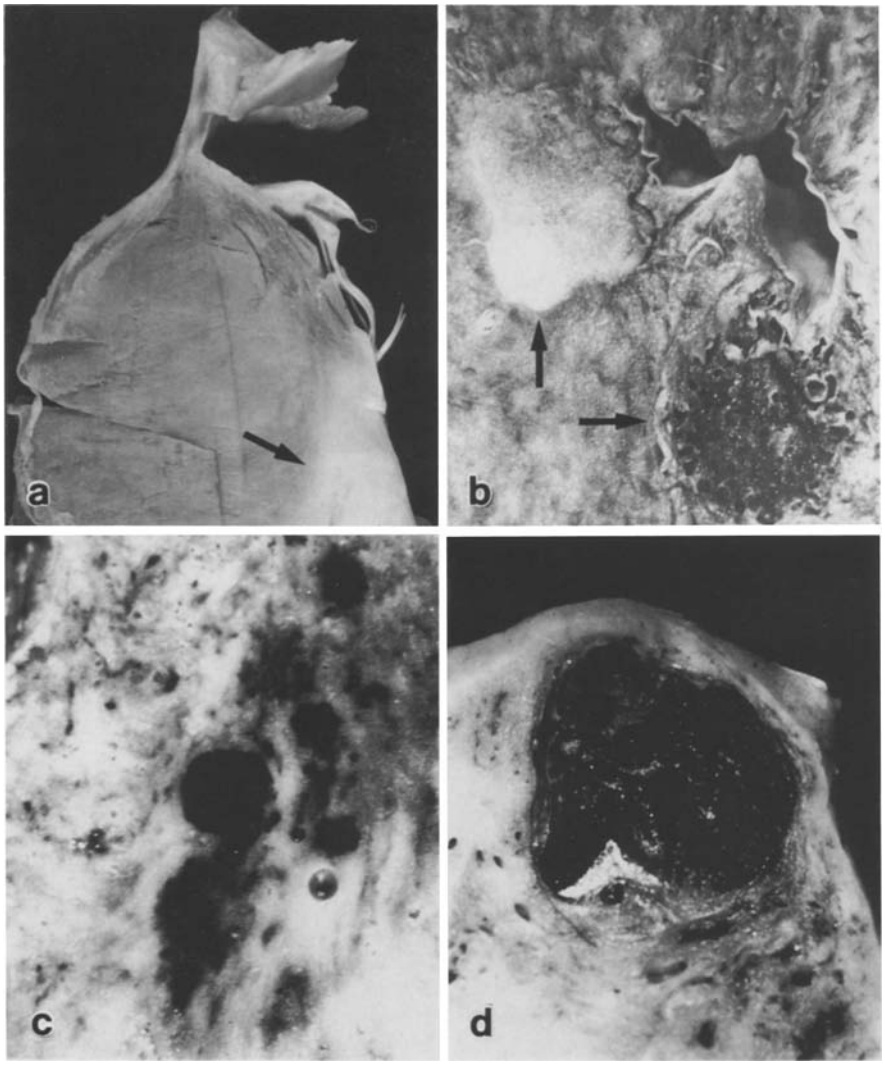

Fig. 1. Macroscopic appearances of heart **a**, liver **b**, renal medulla **c** and uterine fundus **d.** Haemangiomatous lesions (*arrows*) were clearly demarcated from the surrounding tissue in each organ

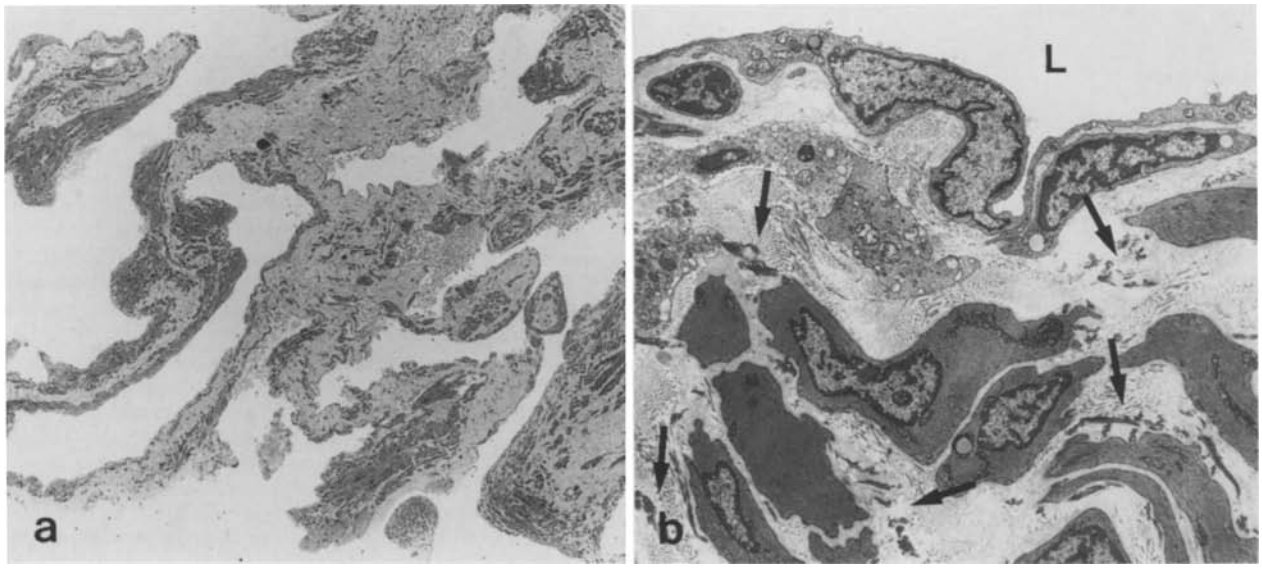

Fig. 2a, b

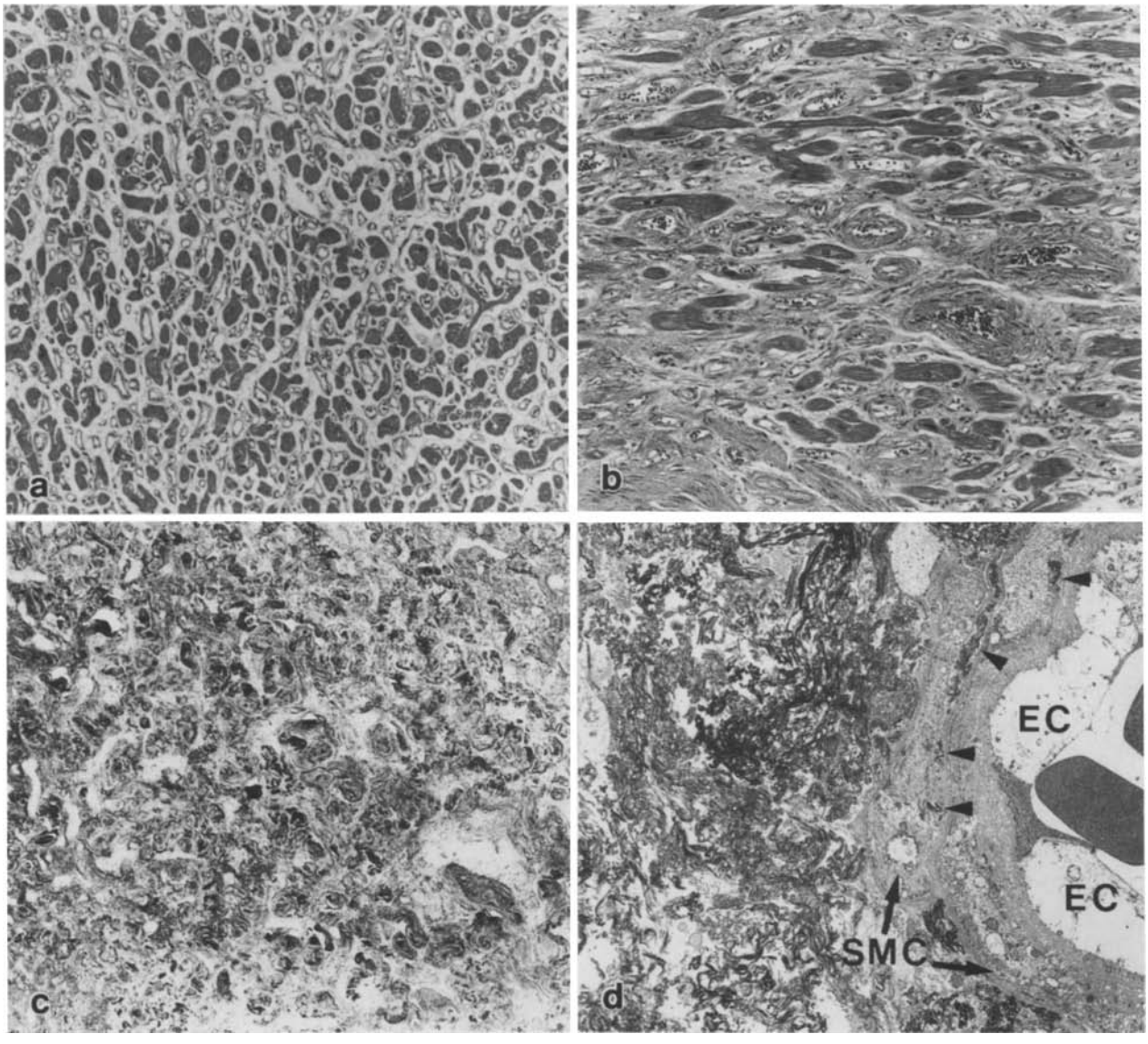

Fig. 3. (**a**) Cardiac haemangioma. The vascular lumina are small, being almost the capillary size, and they are intermingled with the original myocardial tissue. (H&E ×110) **b** Cardiac haemangioma. The size of vascular lumina are somewhat larger than that of **a**. The vascular wall is well-developed with some layers of smooth muscle cells. (H&E ×110) **c** Light microscopy of tumour that was macroscopically white and rubbery in the liver. (Elastica van Gieson ×50) **d** Electron microscopy of **c**. Fibers stained darker are aggregate of elastic fibers, and the other fibrous component is collagen fibrils. Elastic fibers also exist between basement membrane and smooth muscle cell of vascular wall (*arrow heads*) (×4100). *EC*: endothelial cell, *SMC*: smooth muscle cell

(1 cm diam.) consisting of numerous vascular lumina separated by thin white septae (Fig. 1b). Similar blood pools were found one each (1.0 cm diam.) in medulla of both kidneys (left 100 g; right 90 g) (Fig. 1c), six in the ileal submucosa (0.5 to 1.5 cm diam.) and one in the uterine fundus (1.5 cm diam.) (Fig. 1d). These blood pools consisted of numerous lumina separated with thin white fibrous septae. The left adrenal gland was enlarged to 8×8×6 cm and had become spherical with the remaining

Fig. 2. Skin. (**a**) 1 μm section of resin embedded subcutaneous cavernous haemangioma. Vascular space is widely dilatated, having several layers of smooth muscle cells. Toluidine blue stain. (×40) (**b**) The vascular wall. Vascular lumen (*L*) is lined with a layer of endothelium. Smooth muscle cells are seen among collagen fibrils and elastic fibers (arrows) (×3200). Elastic and collagen fibers are stained by triple stain method for simultaneous augmentation of elastic and collagen fibers (Yoshihama et al. 1986). All the specimens for electron microscopy in this study were stained by this method

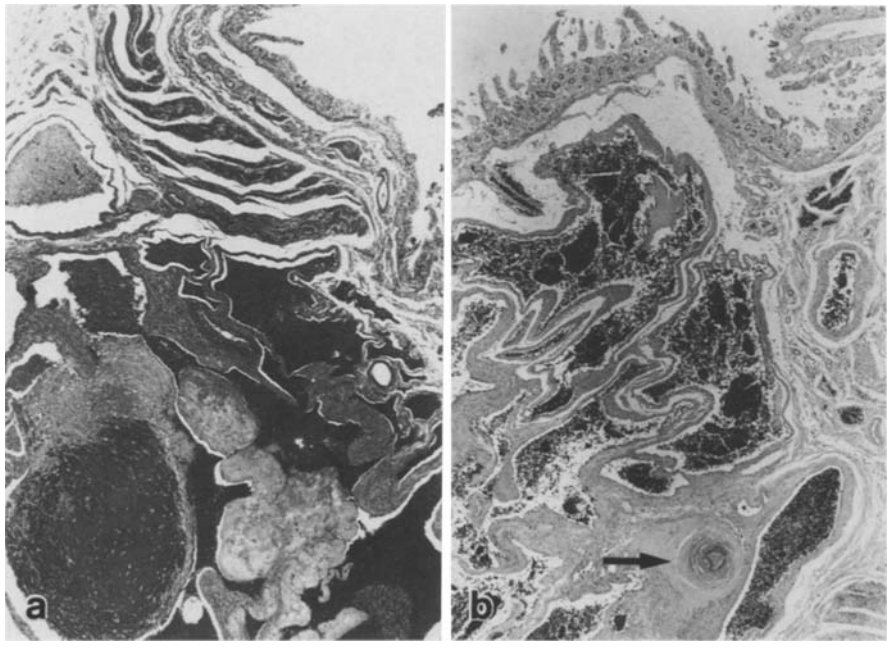

Fig. 4. Ileum. (**a**) Cavernous haemangioma is seen in the propriate muscle layer. Organizing thrombi occlude the vascular lumen partly. (H&E ×20). (**b**) The vascular wall of cavernous haemangioma in the other site is partly calcified (*arrow*) (H&E ×20)

original atrophic adrenal gland. The cut-surface was bright yellow and was entirely covered with fibrous capsule. The right adrenal gland was normal.

No particular lesion was found in the other organs including the cerebral tissue.

Microscopically, the subcutaneous tumours consist of aggregate of vascular channels distended. Each vascular structure is lined by a flattened endothelial cell layer which is supported by spindle-shaped cell layers (Fig. 2a). By electron microscopy, these cells are smooth muscle cells surrounded by basement membrane. There are abundant collagen and elastic fibers among them (Fig. 2b). The diagnosis of cavernous haemangioma is confirmed from these findings. At the site of cardiac tumour, the myocardium is intermingled with many vascular channels comprising capillary and larger vascular lumina which are supported by one or several layers of spindle-shaped cells (Fig. 3a, b). The latter predominate in this tumour. By electron microscopy, the vascular lumina lined by flattened endothelium are supported by one or more layers of smooth muscle cells. The white nodule in the liver consists of aggregate of collagen and elastic fibers (Fig. 3c). Within this nodule, there are many vascular channels of which lumens are mostly obliterated or degenerated. By electron microscopy, such blood channels are lined with a endothelial cell layer supported with some smooth muscle cell layers and the interstitium consists of fine collagen fibrils and elastic fibers (Fig. 3d). The structure of reddish nodule is similar to subcutaneous tumours.

All the blood pools in the ileum, both kidneys and uterus are also cavernous haemangiomas. In the ileal haemangiomas, the lumina are partly occluded by thrombi, and the perivascular interstitium is fibrous with abundant collagen and elastic fibers accompanied by occasional calcification (Fig. 4). The left adrenal gland is replaced by a phaeochromocytoma.

Discussion

Bean (1958) described three forms of vascular lesions in BRBNS: 1) large cavernous haemangioma which replaces the vital structures or obstructs the passage in the alimentary or respiratory tract; 2) compressible blood sac covered by milk-white skin resembling a blue rubber nipple; 3) irregular blue marked spots of which borders merge into the skin. The cutaneous tumours in our case are compatible with the third type. Despite the usual occurrence of haemangioma in the gastrointestinal tract, internal involvement has been also reported in the oropharynx (Sakurane et al. 1967), naso-pharynx (Fretzin and Potter 1967), oral cavity (Baiocco et al. 1984), oesophagus (Rice and Fischer 1962), lung (Rice and Fischer 1962), heart (Nakashima et al. 1983), liver (Bean 1958; Rice and Fischer 1962), spleen (Rice and Fischer 1962), peritoneal cavity (Rice and Fischer 1962), brain (Waybright 1978; Gallmann and Boltshauer 1987), eye (Crompton and Taylor 1981; Rennie et al. 1982), joint (McCarthy et al. 1982) and penis (Smart and Newton 1975; Wong and Lau 1982).

Our patient had suffered from chronic heart failure for some time and died of this condition. Although primary cardiac haemangioma is rare (McAllister and Fenoglio 1978), solitary haemangiomatous lesion was found in our patient. The size of the vascular lumina of the myocardial haemangioma in our case varied. Haemangiomas have been classified traditionally by the size of vascular lumen. If we judge the present cardiac haemangioma from this standpoint, it seems appropriate to consider it as between a capillary and cavernous haemangioma. By electron microscopy, the vascu-

lar wall was often supported by some smooth muscle cell layers. It is reported that cavernous haemangioma has much more heavily collagenized vascular septae containing multilaminar smooth muscle cells when compared with capillary haemangioma (Iwamoto and Jakobie 1979). Mixed haemangiomas which demonstrate features of both capillary and cavernous haemangiomas has also been reported (Garcia and Dixon 1984; Rothstein et al. 1985). The large lumen and thick vascular wall with smooth muscle cells which predominate in the present cardiac haemangioma may indicate that this tumor should be classified as the mixed-vessel (capillary-cavernous) type of haemangioma.

Apart from the cardiac haemangioma, phaeochromocytoma was detected at autopsy without ante-mortem catecholamines measurement, however, the patient's blood pressure level was known to be low from the clinical history. In addition, neither myocardial haemorrhage (Kline 1961), scar (Sjoerdsma et al. 1966) nor calcium deposition (Buja et al. 1976) was seen in the heart. It seems that this tumour was biologically inactive.

The two hepatic tumours found in our case are superficially different in macroscopic appearances. The reddish tumor is a typical cavernous haemangioma, while the grayish white nodule consists of collagen and elastic fibers, and of many obliterated vascular channels which are lined by a endothelial cell layer supported by some smooth muscle cells. We interpreted these findings as slcerosis of cavernous haemangioma. Either sclerotic or calcific degeneration of the haemangiomas revealed in the liver and ileum in our case may be due to natural progression (Schiff 1975; Nakagawara et al. 1977; Anthony 1979; Berry 1985).

In the present case, the kidney and uterus were also involved by cavernous haemangioma. We interpreted all the vascular tumours in our case to be cavernous haemangioma with the exception of the cardiac tumour, on the basis of our own and these reported findings. The primary occurrence of haemangioma is unusual in the kidney (Bell 1938) and uterus (Pedowitz et al. 1955). It is likely to be involved by haemangioma in those organs in BRBNS under which haemangioma may occur in any organ.

The vascular lesions in BRBNS have been variously reported as cavernous (Fretzin and Potter 1965; Walshe et al. 1966; Baker et al. 1971; Kumakiri et al. 1981), capillary haemangiomas (Hagood and Gathright 1975), glomus tumours (Chandon et al. 1978; Gilardi and Harms 1982), haemangioendothelioma (Kumakiri et al. 1981) and arteriovenous fistulae (Waybright et al. 1978; Nakashima et al. 1983). Capillary and cavernous haemangiomas, venous angioma, arteriovenous malformations and Galen's venous aneurysm have occurred in one individual (Rosenblum et al. 1978). Despite frequent occurrence of cavernous haemangioma, it seems natural that any type of vascular tumour may occur in BRBNS. It is important to note that BRBNS was originally designated as a syndrome in which the examination of internal organs is required where suspicious skin lesions are seen.

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