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ORIGINAL ARTICLE

Hormonal receptors in cutaneous vascular malformations: 51 cases

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Abstract

Vascular malformations (VMs) are rare congenital anomalies that develop during embryogenesis in different types of vessels. Several triggering factors of cutaneous VMs include trauma, infections, or hormonal changes. We investigated the expression of hormonal receptors (androgen, estrogen, progesterone) in tissue samples of well-characterized VMs. A secondary objective was to identify self-reported triggering factors for these VMs, including hormonal changes, in the cohort of patients. We included patients with VM samples obtained in the tertiary center for vascular anomalies of the University Hospital Center of Tours, France, from January 1, 2007, to August 1, 2018. Immunohistochemistry was used to detect the expression of hormonal receptors (estrogen, progesterone, androgens). We obtained 51 samples from 51 patients: 13 cystic lymphatic malformations (CLMs), 16 venous malformations (VeMs), 11 arteriovenous malformations (AVMs), 4 combined VMs, 4 *PIK3CA*-related overgrowth spectrum, 1 Parkes-Weber syndrome, 1 Gorham syndrome, and 1 multiple lymphangioendotheliomatosis with thrombopenia. In total, 38 (74.5%) samples were positive for androgen receptor: 11 (84.6%) CLMs, 12 (75.0%) VeMs, 8 (72.2%) AVMs, and 7/11 (63.5%) other samples. All samples were negative for estrogen and progesterone receptors. Triggering factors were self-reported in 7 cases and were most frequently hormonal changes ($n = 6$, 18.2%). Hormonal triggers were frequent in AVMs ($n = 4$). Among patients with identified hormonal triggers, VM samples were positive for androgen receptor in 3 and negative in 3. Three-quarters of our VM samples expressed androgen receptor, and most CLM, VeM, and AVM samples were positive. Hormonal triggers were identified in 6/33 patients, mostly with AVMs.

Keywords Vascular malformations · Hormonal receptors · Androgen receptors · Hormonal triggers

Introduction

Cutaneous vascular anomalies include vascular tumors, mainly represented by infantile hemangiomas, and vascular malformations (VMs), which are rare congenital anomalies that develop during embryogenesis in different types of vessels (i.e., capillaries, lymphatic vessels, veins, or arteries) [1]. The International Society for the Study of Vascular Anomalies guidelines classifies VMs by type of vessel: simple VMs, combined VMs, VMs of major vessels, or VMs associated with other anomalies [2].

Advances in molecular biology have allowed for better understanding the pathogenesis of VMs. VMs might be syndromic or familial, transmitted by germinal mutations (e.g., capillary malformation-arteriovenous malformation syndrome, which is caused by germinal *RASA1* or *EPBH4* mutations) [3, 4]. A number of VMs, especially those with segmental distribution, are linked to post-zygotic mutations, affecting apoptosis, maturation, or growth of vascular cells [5]. Capillary malformations linked to Sturge-Weber syndrome showed somatic mutations of *GNAQ* [6, 7], and venous malformations (VeMs) showed somatic mutations of *TIE2* or *PIK3CA* [8–10]. Cystic lymphatic malformations (CLMs), especially those associated with overgrowth belonging to *PIK3CA*-related overgrowth spectrum (PROS), have shown post-zygotic mutations of *PIK3CA* [9,

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11]. A recent publication reported *MAP2K1* mutations in extracranial arteriovenous malformations (AVMs) [12].

Cutaneous VMs often occur during childhood but might appear later in life. In most cases, the diagnosis is suggested by physical examination and is supported by imaging. Biopsies are rarely needed. Management might involve no treatment, physical therapy, various drugs, sclerosis, or surgery and depends on the VM type, location, size, and staging as well as the patient's age [13, 14]. The natural history of VM differs by VM type. VMs can increase in volume progressively or by flares. Capillary malformations might remain stable during life or become progressively hypertrophic [15]. CLMs might decrease in size, when macrocysts undergo sclerosis after locoregional infections during infancy, or might progress during adolescence, especially if they are microcystic lymphatic malformations [14, 16]. VeMs usually progressively increase in volume throughout life [17]. AVMs also progress by flares, especially after puberty [18]. Several triggering factors suggested for cutaneous VMs include trauma, infections, or hormonal changes [19, 20]. Pregnancy and puberty have been reported to trigger progression of CLMs, VeMs, and AVMs in numerous case reports [21–24]. However, we lack data to confirm the effect of hormonal factors on VMs.

In this study, we investigated the expression of hormonal receptors (androgen, estrogen, progesterone) in tissue samples of well-characterized VMs. The secondary objective was to identify self-reported triggering factors for these VMs, including hormonal changes, in a cohort of patients.

Methods

Study design and setting

This monocentric retrospective study included a cohort of patients with VMs followed up in the tertiary center for vascular anomalies of the University Hospital Center of Tours, France. It included patients with VMs for which samples were obtained from January 1, 2007, to August 1, 2018. Data were collected from April 1, 2018, to August 31, 2018.

Participants

We included all patients with a well-identified VM, apart from capillary malformations. They could be CLMs, VeMs, or AVMs, simple, combined, or syndromic. All patients included had to have tissue samples of VMs and a confirmed diagnosis based on physical examination, imaging, and pathology examination. Samples consisted of biopsies for diagnosis or surgically removed lesions. Medical data were collected from patients' medical files. We collected data on demographics (age and sex) and VMs (type, location, treatment, evolution). All included patients or their parents, if under age 18, gave their written agreement to analyze their clinical data and samples. We contacted patients by phone to collect data on triggering factors for their VM and hormonal status.

The study was approved by the institutional review board of CHRU Tours (#2018 067).

Outcomes

The primary outcome was immunohistochemical expression (classified as no expression, slight expression, and strong expression) of hormonal receptors (androgen, estrogen, and progesterone) in samples of each type of VMs. The secondary outcome was the analysis of self-reported triggering factors for each type of VM, collected by phone call and the medical history of patients.

Immunohistochemical techniques and controls

Samples were analyzed by immunohistochemistry at the Department of Pathology of the University Hospital of Tours. Samples were fixed in formalin, then embedded in paraffin, and cut in sections 4 μm thick. Immunostaining involved use of the Automate Benchmark XT (Ventana Medical Systems, Roche). Primary antibodies for estrogen receptor (monoclonal rabbit antibody, clone EP1 DAKO, dilution 1:100), progesterone receptor (monoclonal mouse antibody, clone 16 NOVOCASTRA, dilution 1:100), and androgen receptor (monoclonal mouse antibody, clone SP 107 ROCHE, prediluted) were incubated at 37 °C for 32, 56, and 60 min, respectively. Slides were counterstained for 8 min with hematoxylin, then 4 min with bluing reagent. Positive controls were samples from breast cancer for estrogen and progesterone receptors and from sebaceous carcinoma for androgen receptor. We used non-pathological cutaneous samples from children and adults as negative controls.

Each sample was interpreted by two readers: a pathologist (MCM) and a dermatologist (SV). The density of hormonal receptors was determined at magnification 20 and expressed as no staining, slight staining (+), and strong staining (++). Slight staining was defined as positive for endothelial cells, which was less intense than positive controls and more intense than negative controls; strong staining was considered similar to positive controls for endothelial or media cells. We also assessed whether staining was focal (some endothelial cells) or diffuse.

Study size

We performed no sample size calculation because it depended on the number of available samples. We expected to include at least 10 patients per group.

Statistical issues

Descriptive data are expressed as mean ± SD for quantitative data and number (%) for categorical data.

Results

Characteristics of participants and VMs (Table 1)

Overall, 333 tissue samples were eligible. We excluded 16 samples addressed to our center for expertise, because no clinical data were available; 21 duplicates (same VM with 2 or more samplings); 208 samples of vascular tumors; and 37 samples for which diagnosis remained doubtful. Finally, 51 samples from 51 patients were included; 33 (64.7%) patients could be reached by phone for collecting clinical data.

The cohort consisted of 32 males (62.7%) and 33 children (64.7%); the mean age at sampling was 14.4 years ± 15.0. Among the 51 samples, 40 were simple VMs (78.4%):13 were CLMs (25.5%), 16 VeMs (33.4%), and 11 AVMs (21.6%). Among the 11 other cases, 4 were combined VMs (2 veno-lymphatic and 2 capillaro-veno-lymphatic), 4 were PROS, 1 was Parkes-Weber syndrome, 1 was Gorham syndrome, and 1 was multiple lymphangioendotheliomatosis with thrombopenia (MLT).

The most frequent locations of simple VMs were head and neck ($n = 24$, 47.1%) and limbs ($n = 20$, 39.2%). Doppler ultrasonography was performed in 11 patients (21.6%) to support the diagnosis and MRI in 35 patients (68.6%). VMs were surgically removed in 35 (68.6%) patients, and sclerosis was performed for 19 VMs (36.5%). Overall, 26 (50.9%) patients had multiple therapies, including surgery, sclerosis, and background drug treatment. The drugs used were oral steroids ($n = 2$), aspirin ($n = 2$), propranolol ($n = 4$), and oral sirolimus ($n = 6$).

Primary outcome

In all, 38 samples (74.5%) were positive for androgen receptor: 11/13 (84.6%) CLMs, 12/16 (75.0%) VeMs, 8/11 (72.2%) AVMs (Fig. 1), and 7/11 (63.6%) other VMs. Details are in Table 2. VMs were positive for androgen receptors in 25 out of 32 males (78.1%), and in 13 out of 19 females (68.4%). The staining for androgen receptor was strong in 20 samples (39.2%). Among the 38 positive samples for androgen receptor, the staining was diffuse for 34 samples (89.5%) and focal for 4 (10.5%): 2 CLMs and 2 VeMs. All samples were negative for estrogen and progesterone receptors.

In 15 cases, sclerotherapy was performed before surgical removal of the VM. Among them, 10 were positive for androgen receptor (66.7%). Two patients received drugs before

Table 1 General characteristics of patients with vascular malformations

	n	Male *n*, %	Age at diagnosis, years mean ± SD	Age at end of data collection, years* mean ± SD	Topography *n* (%)				Triggering factors* *n* (%)			Treatment type *n* (%)		
					He	Li	Tr	Gl	Hor	Inf	Tra	Surg	Scle	Med
CLM	13	9 (69.2)	0.9 ± 1.9	12.2 ± 5.6	6 (46.2)	6 (46.2)	1	0	1/8	1/8	1/8	12 (9.3)	1 (8.3)	3 (25)
VeM	16	10 (62.5)	2.3 ± 4.8	14.1 ± 3.6	6 (37.5)	6 (37.5)	2	2	0/12	0/12	1/12	16 (100)	7 (43.7)	3 (18.7)
AVM	11	6 (54.5)	18.1 ± 20.5	24.0 ± 11.2	11 (100)	0	0	0	4/7	0/7	0/7	11 (100)	6 (54.5)	1 (9.1)
Others:			2.2 ± 3.9	19.4 ± 9.3								9 (69.3)	5 (41.6)	6 (46.1)
Gorham	1	1				1								1
PROS	4	2		26.2	1	3			0/3	0/3	1/3	4	1	1
MLT	1	1						1						1
PWS	1	1	0.67			1						1	1	1
CLM+VeM	2	1	3	10.5		2			0/2	0/2	0/2	1	2	1
CM+CLM+VeM	2	1	5.5	14.1		1	1		1/1	0/1	0/1	2	1	1
Total	51	32 (62.7)	5.7 ± 12.7	16.5 ± 8.3	24 (27.1)	20 (39.2)	4 (7.8)	3 (5.9)	6 (18.2)	1 (3.0)	3 (9.1)	47 (90.4)	19 (36.5)	13 (25.5)

*Total: 33 patients

CLM cystic lymphatic malformation, *VeM* venous malformation, *AVM* arteriovenous malformation

PROS PIK3CA-related growth spectrum, *MLT* lymphangioendotheliomatosis with thrombopenia, *PWS* Parkes-Weber syndrome

CLM+ VeM combined lymphatico-venous malformation, *CM+ CLM+ VeM* capillaro-lymphatico-venous malformation

He head and neck, *Li* limbs, *Tr* trunk, *Gl* gluteal area, *Hor* hormonal, *Inf* infection, *Tra* trauma, *Surg* surgery, *Scle* sclerosis, *Med* medical

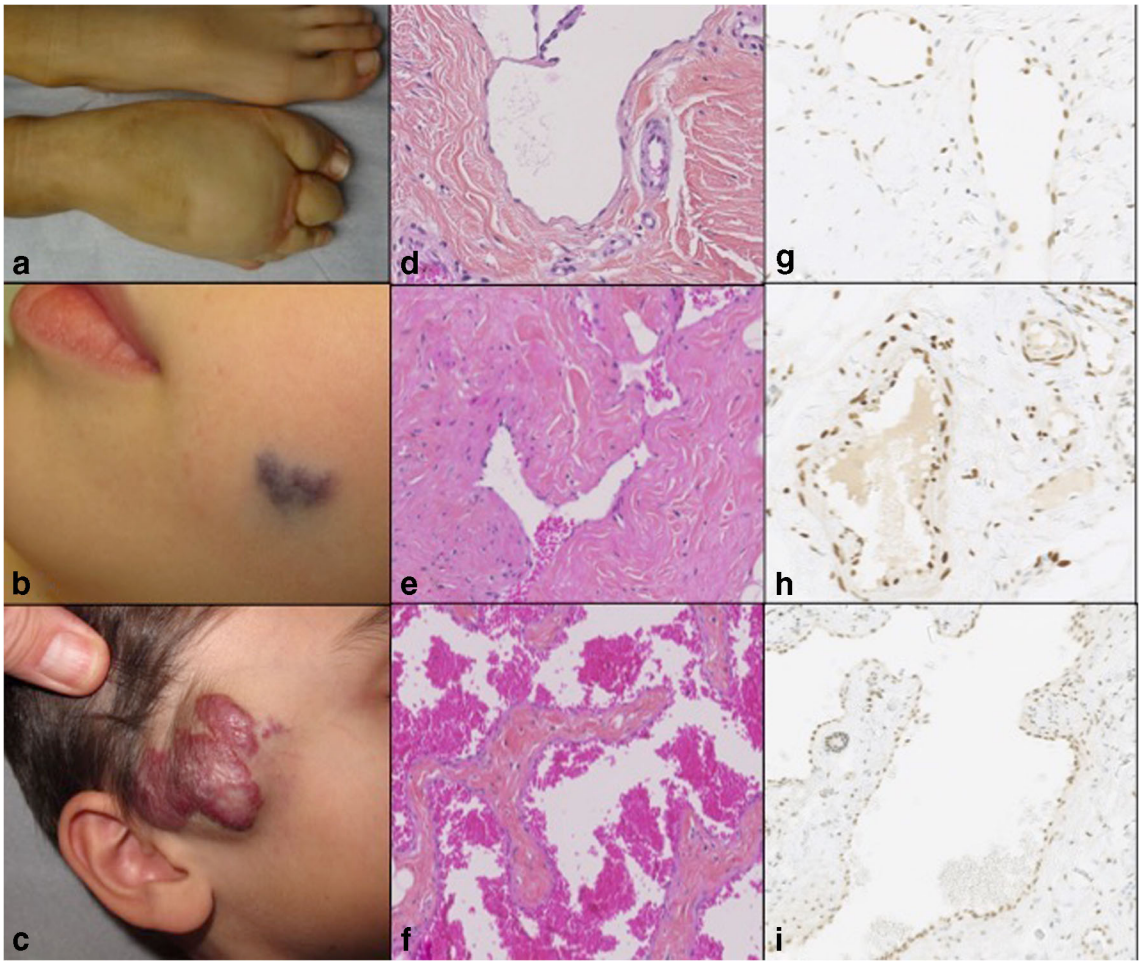

Fig. 1 Clinical features of **a** microcystic lymphatic malformation of the foot, **b** venous malformation of the tongue and lower lip, **c** arteriovenous malformation, H&E image of **d** microcystic lymphatic malformation of the foot, **e** venous malformation of the tongue and lower lip, **f** arteriovenous malformation, **g**, **h**, **i** positive staining for androgen receptor

surgery (propranolol in both cases): one was positive for androgen receptor and one was negative.

Secondary outcome

Mean age at VM diagnosis was 5.7 ± 12.7 years, and mean age at the last follow-up contact was 16.5 ± 8.3 years. Among the 33 patients who answered questions by telephone, self-reported mean age at puberty was 12.7 ± 2.5 years; we found no cases of hirsutism or precocious puberty. Triggering factors were self-reported in 7 cases (21.2%); the most frequent factor was hormonal changes ($n = 6$, 18.2%), including puberty ($n = 5$, 2 were males) and pregnancy ($n = 1$). Hormonal triggers were most frequent in AVMs (4/7 [57.1%] cases with data collected). Data are in Table 1.

Among the 6 patients who identified hormonal triggers, VM samples were positive for androgen receptor in 3 and negative in 3 (Table 2).

Discussion

Key results

In our cohort of 51 samples of well-characterized VMs, three quarters of the VMs expressed androgen receptors. Most samples of CLMs, VeMs, and AVMs were positive for androgen receptor. All samples were negative for estrogen and progesterone receptors. Hormonal triggers were identified in 6 of 33 patients contacted by phone and mostly AVMs ($n = 4$).

Limitations

First, we had a limited number of VMs, as we included only those with confirmed diagnosis. Second, previous interventions for VMs, such as sclerosis, might have modified immunohistochemical findings. Third, we could not find any association between the presence of hormonal triggers and positivity for androgen receptor in VMs, given the small number

Table 2 Expression of hormonal receptor and triggering factors

	n	Age at sampling, years mean ± SD	Estrogen receptor expression *n* (%)	Progesterone receptor expression *n* (%)	Androgen receptor expression *n* (%)		Hormonal triggering factors n (%)	
					+	++	AR+	AR−
CLM	13	7.2 ± 5.3	0	0	11 (84.6)		1 (7.7)	
					7 (53.8)	4 (30.8)	1	0
VeM	16	9.0 ± 3.5	0	0	12 (75)		0	
					4 (25)	8 (50)		
AVM	11	29.7 ± 22.8	0	0	8 (72.2)		4 (36.4)	
					5 (45.5)	3 (27.2)	1	3
Others:	11	15.5 ± 12.4	0	0	7 (63.6)		1	
					2 (18.1)	5 (45.4)	1	0
Gorham	1	12.1				1		
PROS	4	24.1	0	0		2		
MLT	1	0	0	0				
PWS	1	9.2	0	0				
CLM+VeM	2	7.4	0	0	1	1		
CM+CLM+VeM	2	13.5	0	0	1	1	1	
Total	51	14.4 ± 15.0	0	0	38 (74.5)		6 (11.8)	
					18 (35.3)	20 (39.2)	3	3

CLM cystic lymphatic malformation, *VeM* venous malformation, *AVM* arteriovenous malformation

PROS PIK3CA-related growth spectrum, *MLT* lymphangio-endotheliomatosis with thrombopenia, *PWS* Parkes-Weber syndrome, *CLM+VeM* combined lymphatico-venous malformation, *CM+CLM+VeM* capillaro-lymphatico-venous malformation, + slight expression, ++ strong expression, *AR+* positive for androgen receptor, *AR−* negative for androgen receptor

of patients contacted. Also, the self-reported and retrospective nature of the study limited an exhaustive collection of triggering factors because of memory bias.

Interpretation

Our study shows that most VMs, of any type, are positive for androgen receptor, expressed by endothelial or media cells. Our results are similar to those for 36 cutaneous VMs from Liu et al. [25]. However, Kulungowski et al. demonstrated positivity for androgen receptor in less than half of their collection of 11 superficial AVMs (45.5%), very poor expression in 14 VeMs (14.3%), and no expression in 20 CLMs [26]. This discordance could be linked to differences in techniques used and controls. In rare vascular anomalies, such as MLT and Gorham syndrome, we found no expression and strong expression of androgen receptor, which has never been reported.

The positivity for androgen receptor in most of our VMs is not fully understood. It may be linked to the embryologic origin of these malformations because many fetal tissues express androgen receptor, both genital (penis, prostate, testis, epididymis, scrotum, uterus, cervix, and ovaries) and non-genital (lungs, great vessels, trachea, muscles, scalp skin, kidney, thyroid, stomach, bowels, thymus, and ureter). In adult tissues, these receptors are expressed in genital tissues and in some components of skin such as fibroblasts, sebaceous glands, eccrine sweat glands, root sheath of hair follicles, and endothelial and smooth muscle cells of blood vessels [27, 28]. Treatment previous to the surgical removal of the VM (sclerotherapy especially) did not seem to affect the expression of androgen receptor, although samples are too small to allow for a definite conclusion.

Most VMs are linked to post-zygotic mutations, so these mutations might be linked to androgen receptor positivity. Lehmann et al. found *PIK3CA* mutations frequent in triple-negative breast cancer tissue that was positive versus negative for androgen receptor (40% vs 4%). Furthermore, the growth and viability of triple-negative breast cancer cell models positive for androgen receptor were significantly reduced after treatment with PIK3 inhibitors combined with androgen receptor antagonists versus PIK3 inhibitors alone [29]. Recently, Venot et al. demonstrated the efficacy of PIK3CA inhibitors to improve symptoms in 19 patients with severe PROS [30]. If a link is shown between somatic mutations of *PIK3CA* in VMs and expression of androgen receptors, new therapeutic targets could be investigated.

All our VM samples were negative for estrogen and progesterone receptors, which is similar to results by Kulungowksi et al. [26]. However, Duyka et al. found 83% expression of progesterone receptor in their cohort of 12

AVMs of the head, and half of their 8 CLM cases of the head was also positive [31]. In this study, negative controls were archival breast samples and mucosal tissue.

In our study, 18.2% of patients reported that hormonal changes triggered their VMs. This trigger cannot be explained by estrogen or progesterone receptor expression, which was negative, but might be explained by androgen receptor positivity. These VMs could be stimulated by increased androgen secretion during hormonal changes such as puberty, or in case of trauma or infections, secretion of adrenal androgen [32, 33].

Kulungowski et al. showed that CLMs, VeMs, and AVMs express receptors to growth hormone (GH), and hypothesized that GH might contribute to the increase in size of VMs during puberty, when levels are increased [26]. In the same way during pregnancy, placental GH, which binds to the same receptors as GH, could trigger VMs. Increased GH secretion could be also stimulated by estrogen and testosterone secretion during puberty [34]. Another hypothesis is based on expression of follicle-stimulating hormone (FSH) receptor by VM endothelial cells. Maclellan et al. found more positive stained areas of FSH receptor in AVMs (2.65%) than other VMs, where it was < 1%. Despite this low staining density, the authors suggested that FSH might affect the increase in VMs directly by hormonal action or indirectly by another not identified pathway [35]. We did not study the expression of GH or FSH receptor in our cohort.

Conclusion

Here, we show that most VMs are positive for androgen receptor; further investigations should focus on the link between new molecular findings of somatic mutations (*PIK3CA*, *TIE2*, *MAP2K1*) and positivity for androgen receptor. By analogy with in vitro studies on breast cancers, hormonal issues could be addressed by drug strategies to avoid expansion of VMs, especially AVMs.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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