Case Report

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Microvascular proliferation in arteriovenous malformation of the hand worsens during pregnancy: a case report

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Introduction and Importance: Arteriovenous malformations (AVMs) are rare congenital disorders characterized by episodes of disproportionate growth that can cause pain and severe bleeding, with microvascular proliferation (MVP) associated with these episodes. Hormonal influences can also worsen the symptoms in patients with AVM.

Case presentation: This case report presents a female patient with congenital vascular malformations of the left hand since birth, whose symptoms worsened during puberty and pregnancy, ultimately leading to amputation of the left hand due to unbearable pain and loss of function. Pathologic analysis revealed substantial MVP activity within the tissues of the AVM, with an expression of receptors for estrogen, growth hormone, and follicle-stimulating hormone in the vessels of the AVM, including MVP areas. Resected materials not related to pregnancy revealed chronic inflammation and fibrosis but hardly any MVP.

Discussion and conclusion: These findings suggest a role for MVP in the progressive growth of AVM during pregnancy, with a potential role for hormonal influences. The case highlights the relationship between AVM symptoms and size during pregnancy and the pathological findings of MVP areas within the AVM with hormone receptor expression on proliferating vessels in resected materials.

Keywords: arteriovenous malformations, case report, hormones, pregnancy, proliferation, vascular malformations

Introduction

Arteriovenous malformations (AVMs), a subtype of congenital vascular malformations, are rare vascular disorders composed of masses of malformed vessels characterized by direct shunting between arteries and veins. They are caused by localized errors in vascular development during embryonic life[1,2]. Vascular malformations are usually quiescent but can show sudden, episodic growth throughout life[3]. This abnormal growth has been correlated previously with the presence of proliferating capillary vessels [microvascular proliferation (MVP)] within the malformations. Meijer-Jorna *et al.*[4] reported occurrence of substantial MVP in *c.* 30% of a series of resected symptomatic AVM. Furthermore, the signs and symptoms of AVM can worsen during episodes of increasing hormonal activity, including puberty and/or pregnancy[3,5–8]. The diagnosis and treatment of AVM remain a challenge.

In this case report, we present the clinical, radiological, and histological findings of a patient with AVM in the hand presenting with recurrent exacerbations of pain, possibly provoked by elevated hormone levels. We conducted a review of the current literature on increased hormone levels associated with vasoproliferative growth in AVM and performed immunostaining on the

HIGHLIGHTS

- A previously diagnosed arteriovenous malformation (AVM) of the left index finger of a 24-year-old patient was complicated by massive pain and loss of function of the finger during pregnancy.
- Episodes of microvascular proliferation (MVP) have been reported previously in resected (symptomatic) AVM.
- In our case, we confirmed histologically the presence of MVP and receptor molecules for several types of hormones in the vessels of the lesions.
- Increased hormonal activity may affect the progressive growth of the AVM during pregnancy, potentially due to MVP.

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vascular anomalies of our case with antibodies reactive with several types of hormone receptors (HRs). This case report has been reported in line with the SCARE (Surgical CAse REport) 2020 criteria[9].

Case presentation

A female patient of 24 years old was presumed to have capillary malformations on her left hand since birth, which was initially asymptomatic and, therefore, not treated during childhood. At puberty, she experienced pain in the thumb and index finger of the same hand. She did not have any history of drug use, smoking, or allergies. Throughout her life, she had three pregnancies in 1994, 1996, and 2000, during which the symptoms of her hand worsened. In 1997, after delivering her second child, she was admitted to another hospital for evaluation of persistent, intense pain and swelling of the index finger. She then was referred by the general practitioner to our medical center, with extreme pain leading to loss of function of the finger. Clinical examination showed a pulsating swelling of the index finger with a malpositioned joint ('Swan-neck' deformity) and inability to use this finger (Fig. 1). Computed tomography angiography confirmed the radiological diagnosis of AVM (Fig. 2A), and radiograph showed bone destruction on the tip of the left index finger (Fig. 2B). Due to the severity of the symptoms and no options to embolize the malformations radiologically without causing necrosis, amputation of the whole index finger and part of metacarpal-II was performed by a plastic surgeon. After surgery, a specimen of 11×1.8 cm was sent to the pathology department for a histologic examination. Hematoxylin and eosin (H&E) and elastic van Gieson (EvG) staining of selected tissue blocks showed conglomerates of tortuous arteries and intimal thickening, and dilated malformed veins confirming the diagnosis AVM (Fig. 3A, B). In addition, areas of closely packed vasoproliferative microvessels, with plump endothelium and high Ki67 proliferation index, characteristic of MVP, were found amidst the mature blood vessels (Fig. 3C).

In 2001, shortly after her third pregnancy, she returned due to a severely ulcerating and destructive lesion of the distal phalanx of her left thumb, which required a partial resection of the thumb (embolization was again not an option). Unfortunately, the specimen of this surgical resection was not sent in for histological examination. Thereafter, in 2003, due to the unbearable pain and the inability to flex the metacarpal joint, the whole left thumb was amputated. Histologic examination repeatedly confirmed the diagnosis of AVM showing nerve proliferation, interpreted as traumatic neuroma, but no MVP areas were observed.

In 2014, the patient again returned to the clinic with pain located in the residual AVM mass of the distal part of the hand. Therefore, embolization was attempted by an interventional radiologist to close the feeding artery of the lesion. Unfortunately, after embolization, the symptoms of pain and paresthesia worsened, and the patient demanded an amputation of her hand. After long consideration and consultation with the rehabilitation specialist, in 2015, a hand amputation was performed, and the symptoms of pain finally improved after this surgery. Histological examination of the surgical specimen showed, at that time, chronic inflammation, fibrosis, nerve proliferation, occluded arteries, and remnants of embolization materials with foreign body reaction, but a very scarce proliferation of microvessels within the resected AVM. After the left hand amputation, the patient entered a rehabilitation program to practice the use of her remaining left arm. At present, there are no signs of recurrent AVM, but the patient is still suffering from cold intolerance in her left arm. From the patient's perspective, her quality of life has improved greatly because the pain has disappeared.

In order to gain insight into the relationship between the 1997 pregnancy and the lesional proliferative activity, we performed immunohistochemical stainings with antibodies specific for proliferating cells (Ki67) and four types of HRs: estrogen receptor (ER), progesterone receptor (PGR), growth hormone receptor (GHR), and follicle-stimulating hormone receptor (FSHR). They were applied to three lesions available, resected in 1997, 2003, and 2015, which included the left index finger, left thumb, and the whole left hand amputation.

The lesions resected in 1997 and 2015 showed positive expression of ER, GHR, and FSHR in the mature large vessels of AVM and also in the areas of MVP. No expression of PGR was found (Fig. 4). The lesion of the left thumb amputation (2003) showed expression of ER and GHR but differed by lack of FSHR or PGR expression. The timeline illustration to summarize the life events of the patient's history, clinical, and histological findings is shown in Figure 5.

Discussion

In this case report, the patient experienced recurrent, extreme symptoms of her AVM throughout life, particularly during

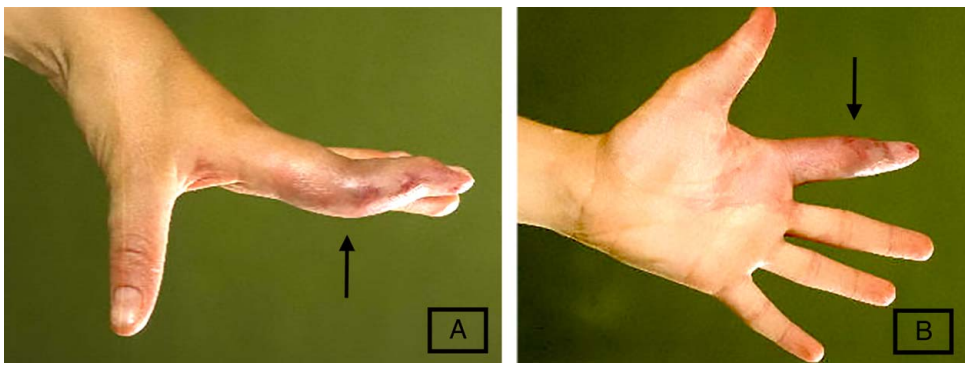

Figure 1. Clinical presentation of arteriovenous malformations on the left hand (A, B). (A) shows a 'Swan-neck' deformity.

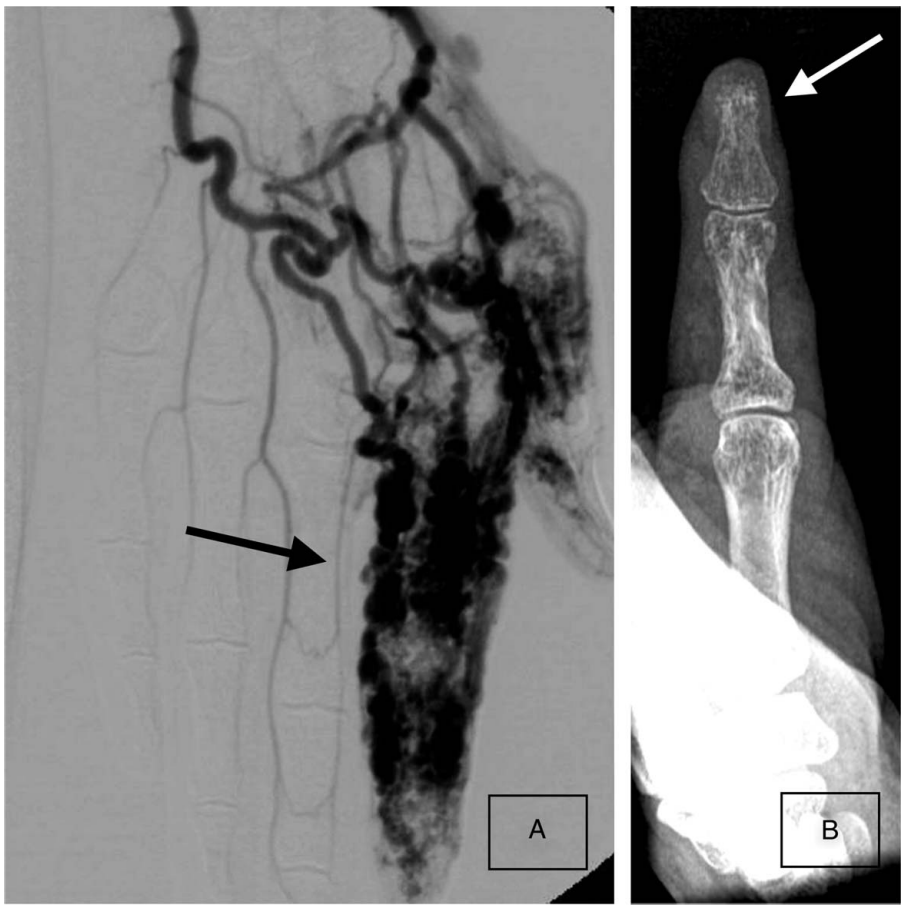

Figure 2. Radiological imaging of the left index finger in 1997. (A) Computed tomography angiography shows the presence of arteriovenous malformations. (B) Radiograph showing bone destruction at the tip of the index finger and affected bone.

episodes of elevated hormonal activity. This suggests a correlation between increased hormonal activity and the progressive growth of AVM.

In 1997, after she delivered her second child, she could not use her index finger anymore because of unbearable pain. Histology of this amputated index finger showed a high proliferative activity of microvessels, and immunostaining confirmed the expression of hormone receptors, such as ER, GHR, and FSHR. The second resection was in 2003, 3 years after her latest pregnancy. At this time, no areas of MVP were found within the lesion, and FSHR was negative. Histology after surgical whole hand amputation in 2015 showed only very scarce proliferative areas that we interpreted as a side effect of postembolization in 2014, as reported previously[3]. However, this lesion also expressed positivity of ER, GHR, and FSHR. We hypothesize that the expression of these hormone receptors in mature vessels and in the interspersed MVP area could play a role in its AVM onset during pregnancy.

Pregnancy is associated with increased levels of hormones, such as estrogen and progesterone[10–12]. Research has further indicated that these hormones may be linked to the expansive growth of congenital vascular malformations[5,13–16]. While the exact mechanism remains unclear, the upregulation of hormone receptors in vascular malformations could take place through several endocrine pathways.

For a long time, the secretory pattern of growth hormone has been studied, and it was reported that the progression from pulsatile to continuous secretion began at the end of the first trimester of pregnancy[17]. Growth hormone is known to possess proangiogenic properties[13] and has a significant anabolic effect on both the mother and the fetus. Additionally, FSH, which chiefly promotes follicular growth and spermatogenesis, has been associated with angiogenesis in vascular malformations[3,14]. A study by Hirano *et al*. showed that FSH secretion was suppressed as a result of increased progesterone and estrogen levels during pregnancy. Furthermore, follicle-stimulating hormone (FSH) levels elevate 10 days after birth, and this correlates with the decrease in sex hormones. In this context, it has been shown that the decline of sex hormones after delivery serves as negative feedback, allowing for the full restoration of reproductive function 2 months after childbirth[18].

Several studies have suggested that progesterone will probably contribute to a larger size and increased flow of AVM, as it has been correlated to increased venous distensibility during pregnancy[19,20]. However, in the current case, immunohistochemistry showed no positivity of PGR on the vessels of the lesion and, therefore, likely exerts hemodynamic effects only. On the other hand, a positive expression of ER was found in our case. A study by Soldin *et al*.[21] reported that serum estradiol increases throughout pregnancy and then remains steady. Concerning its

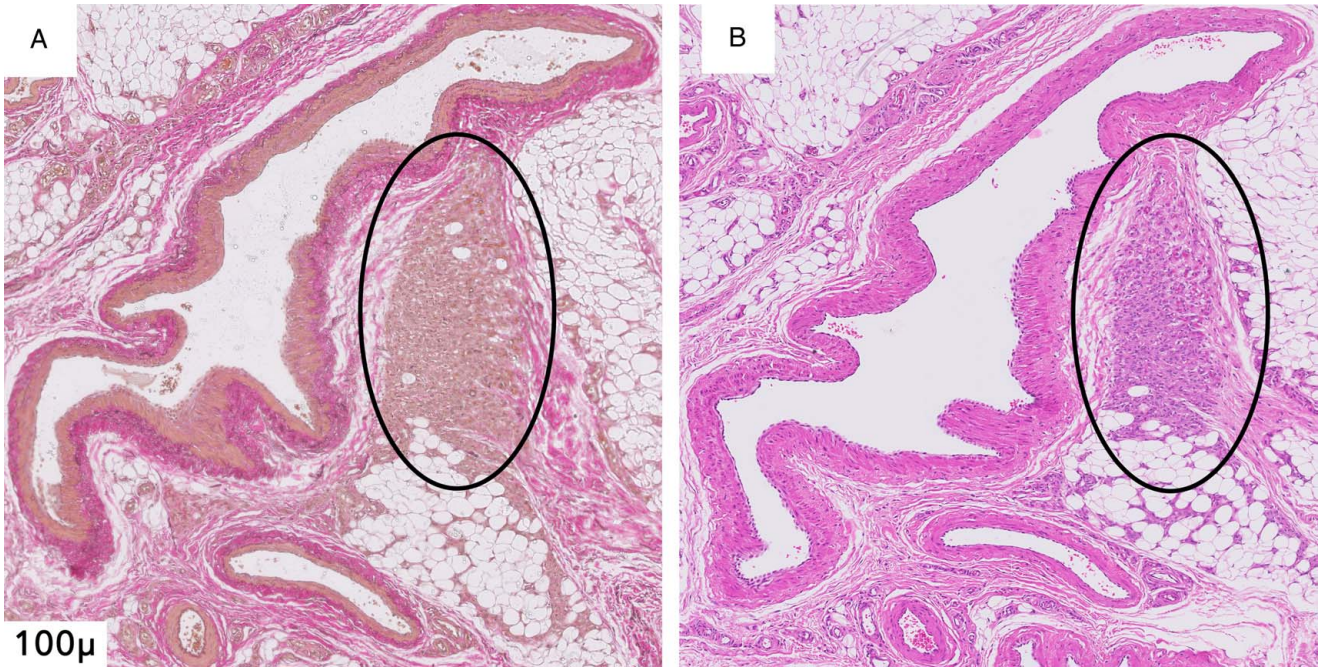

Figure 3. Histology of part of the resected arteriovenous malformation specimen in 1997, stained with (A) elastic van Gieson and (B) hematoxylin and eosin staining. (A) and (B) showing a conglomerate of mature but malformed arteries and veins of arteriovenous malformation and an area of microvascular proliferation (ellipse).

functions, estrogen has been shown to play multiple roles in the maintenance of pregnancy and the maturation of vital organs such as mammary glands for breastfeeding[22].

In a review by Qiao *et al*.[23], it was suggested that hormonal and biomechanical stimulation might significantly contribute to the pathogenesis of AVM. In other studies, it was found that AVM is hormone sensitive and may increase its size and flow in response to hormonal changes[6–8,19,24–26]. As a result, they may enlarge during puberty and/or pregnancy.

To support our hypothesis, we reviewed the literature on the association between hormone activity and the progression of vascular malformations, specifically AVM (Table 1). The earliest case was in 1985, reported by Elliott *et al*.[8], was a 28-year-old woman with swelling, pain, and cyanosis on her left arm during

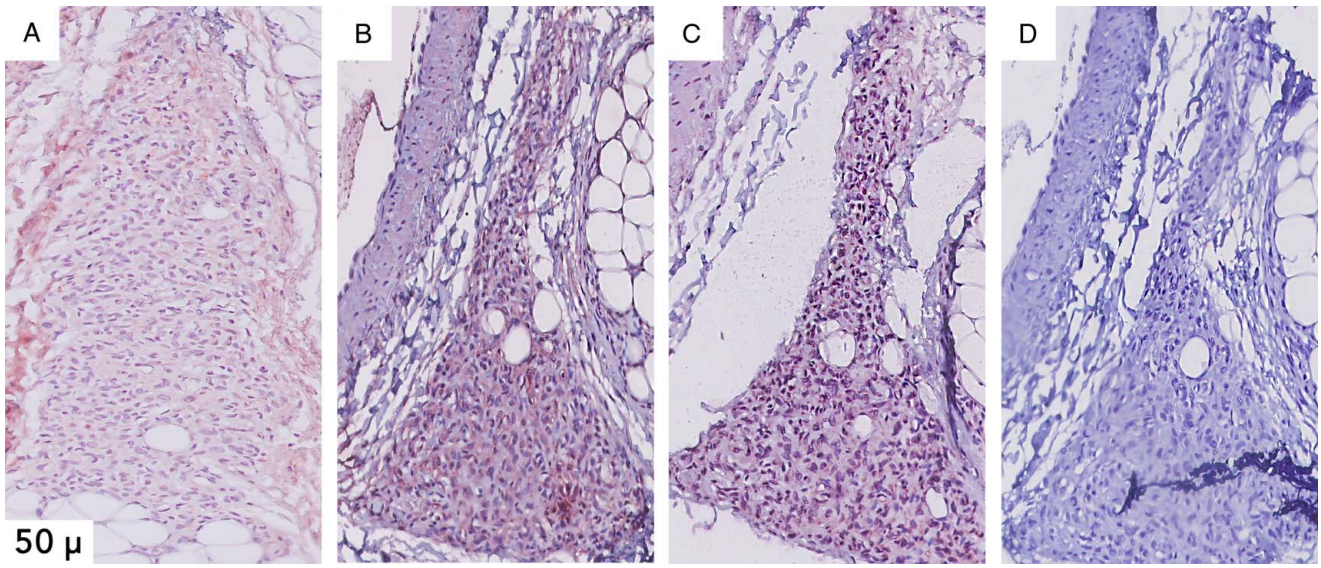

Figure 4. Immunohistochemistical staining of microvascular proliferation area within the arteriovenous malformation in 1997 resected specimen, showing positive expression of estrogen receptor (A), growth hormone receptor (B), and follicle-stimulating hormone receptor (C), but no expression of progesterone receptor (D).

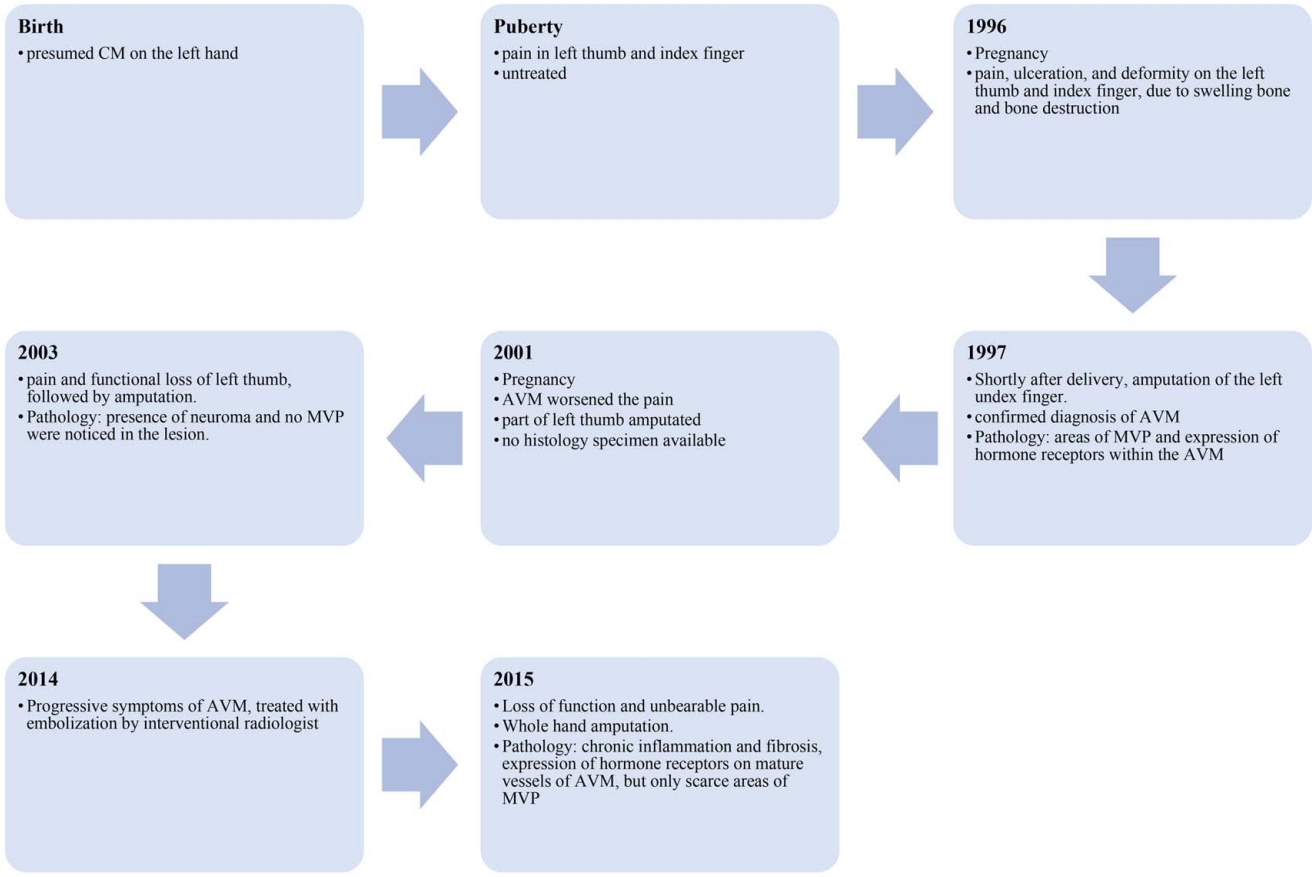

Figure 5. The timeline of the events to present the history, clinical, and histological findings of the patient throughout her life. AVM, arteriovenous malformation; CM, capillary malformation; MVP, microvascular proliferation.

her 18 weeks of gestation. A Doppler ultrasound confirmed its diagnosis of AVM, and the patient was discharged. Later, at the age of 22 weeks gestation, her symptoms worsened with ulcerations and muscular atrophy of the left hand, and signs of congestive heart failure. Since the patient's condition improved dramatically after delivery, the authors speculated on a potential hormonal dysbalance in the course of the disease. In 2011, Pangan[24] reported a case of a 31-year-old woman with enlargement of a left external ear AVM during pregnancy.

In 2019, two cases of AVM worsening during pregnancy were reported. Besson *et al.*[6] described a 40-year-old woman who presented with acute left lower limb edema and dyspnea at 25 weeks of gestation. A magnetic resonance angiography was performed and showed four locations of AVM, two in each thigh. These lesions expanded progressively during the second trimester of pregnancy. In the same year, Fujimaki and Takeuchi[25] documented a case of a 32-year-old woman with recurring swellings of the fingers during pregnancy. A contrast-enhanced computed tomography scan confirmed AVM. The most recent case of an extracranial AVM worsening during pregnancy was reported by Azis *et al.*[7] in 2022, describing a 35-year-old woman with a history of AVM of the forehead since childhood who was admitted to the emergency department with bleeding. During her previous two pregnancies, the lesion had expanded massively in size.

The vascular anomalies listed in our review have been reported during puberty, adolescence, and menopause, and were located in different topographic locations of the body. However, with respect to hormonal changes, the literature specifically highlights the cases of uterine AVM. They tend to occur predominantly in women of reproductive age, and pregnancy appears to play an important role in the pathogenesis of uterine AVM[29]. In a case report published by Nonaka *et al.*[16], the uterine AVM lesion completely disappeared after 6 months of treatment with a gonadotropin-releasing hormone (GnRH) agonist. In the endometrium, the presence of ER in the endothelium suggests that estrogens can mediate endothelial cell proliferation and differentiation. Therefore, it is likely that antiestrogen drugs may have effects on the proliferation of uterine AVM[30]. It is also possible that a decrease in the uterine blood flow and the histologic changes in the blood vessels after the use of a GnRH agonist may arise because of hypoestrogenism, and these changes may also have a favorable effect on a uterine AVM[28,31].

Of interest, there are three studies reporting on the regression of the growth of vascular malformations after pregnancy[8,19,20]. Although the exact reason for the regression is still speculative, it could be due to the changes in the hormonal balance during and after pregnancy[8].

Conclusion

We presented the case history of a patient with an AVM of the left thumb and index finger, showing progressive growth and

Table 1

Overview of 13 studies included in the literature review of hormonal influences related to the vasoproliferative growth of AVM, assessed with Newcastle–Ottawa Scale (NOS)[27].

Number	References	Samples (*n*), mean age, F : M	Main findings	Quality assessment using NOS			
				Selection	Comparability	Output	Time
1.	Elliott *et al.*[8]	Case report of a 28-year-old woman who presented at 18 weeks gestation with a 2 weeks history of increasing swelling, pain, and cyanosis of the left arm	Pregnancy can have a markedly adverse effect on vascular malformations due to hormonal imbalance	★	★	★	Fair
2.	Duyka *et al.*[5]	12 people, 8 females, 4 males with AVM	10 of the 12 AVM samples (83%) stained positive for PGR compared to control ($P < 0.001$)	★	★	★	Good
3.	Pangan[24]	Case report of a 31-year-old woman, 24 weeks pregnant with enlarging left external ear mass	The diagnosis of AVM was considered, and the patient was closely monitored through her 39th week of pregnancy for any potential bleeding, which usually happens to women with AVM during pregnancy	★	★	★	Good
4.	Nonaka *et al.*[16]	Case report of a 30-year-old woman presented with persistent vaginal bleeding, a uterine arteriovenous malformation was diagnosed	Gonadotropin-releasing hormone agonist therapy has the potential to be a conservative treatment modality for uterine arteriovenous malformations in hemodynamically stable patients	★	★	★	Fair
5.	Kulungowski *et al.*[13]	Prospective, 54 patients AVM ($n = 11$)	GHR expression was increased in AVM compared to control ($P = 0.01$)	★	★	★	Good
6.	Durrington *et al.*[26]	Case report of a 29-year-old pregnant woman with frequent nosebleeds	The patient described early onset varicose veins, as did her parents, and this has recently been reported in a series of patients with proven CM–AVM	★	★	★	Good
7.	Maclellan *et al.*[14]	AVM ($n = 10$); no mention of sex	FSHR expression was increased in AVM compared to other vascular anomalies	★	★	★	Good
8.	Katano *et al.*[28]	Case report of a 20-year-old woman presented uterine arteriovenous malformations with congenital heart disease	After the 1-year administration of the GnRHa (11 times), transvaginal ultrasound and MRI showed the disappearance of the uterine AVM lesion	★	★	★	Fair
9.	Besson *et al.*[6]	Case report of a 40-year-old pregnant woman with multiple AVM	The course of the pregnancy was marked by gradually increasing pain in the left thigh and then within the following hours after delivery, we observed a very rapid involution of all AVMs	★	★	★	Fair
10.	Ventéjou *et al.*[15]	51 samples of vascular malformations; 32 males and 19 females	38 (74.5%) samples were positive for androgen receptor: 11 (84.6%) CLM, 12 (75.0%) VMs, 8 (72.2%) AVM, and 7/11 (63.5%) other samples	★	★	★	Good
11.	Srivastava *et al.* [19]	Case report of a 29-year-old woman at 26 weeks of gestation with a case of high-output heart failure secondary to enlarging vascular malformations in the setting of multiple gestation pregnancy	Acute decompensated high-output heart failure in pregnancy due to congenital vascular malformations is rare and can pose significant management challenges	★	★	★	Fair
12.	Fujimaki and Takeuchi[25]	Case report of a 32-year-old pregnant woman with swelling and burning sensation of the finger	In pregnant patients with AVM the likelihood of disease progression during pregnancy must be considered, as well as treatment strategies and timing	★	★	★	Fair
13.	Azis *et al.*[7]	Case report of a 35-year-old woman. During her previous two pregnancies, the lesion expanded in size	Pregnancy tends to accelerate the nature of AVM progression, which can lead to undesirable complications, especially in the head and neck region	★	★	★	Fair

AVM, arteriovenous malformation; CLM, Capillary Lymphatic Malformation; CM, capillary malformation; FSHR, follicle-stimulating hormone receptor; GHR, growth hormone receptor; GnRHa, gonadotropin-releasing hormone agonist; MVP, microvascular proliferation; PGR, progesterone receptor; VMs, venous malformations.

unbearable pain during pregnancy, finally resulting in a complete hand amputation later in life. This disproportionate growth of AVM correlated with MVP activity, as was confirmed histologically. Expression of hormone receptors such as ER, GHR, and FSHR was discovered not only in the mature vessels of AVM but also in MVP areas within the resected lesions shortly after pregnancy. These findings, along with the outcome of our literature search, may suggest a relationship between elevated hormonal levels during pregnancy and the rapid progressive growth of AVM. Future research is needed to further investigate the role of endocrinologic changes in the progression of vascular malformations.

Ethical approval

The study involved leftover materials from the patient that were reviewed and approved by the Medical Ethical Board and Pathology Biobank of Amsterdam University Medical Center (Project number: METC Amsterdam UMC 2022.0873).

Patient consent

Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

A.M.U., S.E.R.H., A.C.W., and C.M.A.M.H.: conception and design of the case report; A.M.U., S.E.R.H., L.B.M.-J., I.S.E.W., O.J.B., A.C.W., and C.M.A.M.H.: acquisition, analysis, and interpretation of data; A.M.U., S.E.R.H., L.B.M.-J., I.S.E.W., O. J.B., A.C.W., and C.M.A.M.H.: drafting the article and revising it critically for important intellectual content. All authors approved the submission of the article.

Conflicts of interest disclosure

The authors declare that they have no financial conflict of interest with regard to the content of this report.

Research registration unique identifying number (UIN)

1. Name of the registry: not applicable.
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Guarantor

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