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Case Report

The relationship between vaginal cavernous hemangiomas and late pregnancy. A case report and a review of the literature

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Summary

The occurrence of cavernous hemangiomas in the vagina is very rare. A 34-year-old woman at 33 weeks' gestation was admitted with a large reddish mass of approximately 5 cm in diameter in the vagina, with bleeding and a sensation of discomfort with walking. The vaginal mass was excised to confirm the pathological diagnosis. Histopathological analysis showed various dilated vessels lined by increased endothelial cells, and the final diagnosis was vaginal cavernous hemangioma. The immunohistochemical analysis showed positive expressions of vascular endothelial growth factor (VEGF), estrogen receptor (ER), and progesterone receptor (PgR) in perivascular stromal cells around the hemangioma. Additionally, the authors reviewed the relationship between genital hemangiomas and pregnancy from the literature. In the female genital tract, six (75%) of eight vaginal hemangiomas were associated with pregnancy, in particular, late pregnancy, in addition to the present case, and eight (32%) of 25 cervical hemangiomas were seen in late pregnancy. Taken together, the hormonal status in late pregnancy may affect the formation of vaginal hemangiomas.

Key words: Vagina; Hemangioma; Hormonal status; Pregnancy.

Introduction

The occurrence of hemangiomas in the female genital tract, particularly in the vagina, is very rare [1]. In this article, the case of a 34-year-old woman (gravida 2, para 1) who presented at 33 gestational weeks with a vaginal cavernous hemangioma is presented. There have been several previous case studies that reported the rapid proliferation and complete resolution of female genital hemangiomas related to pregnancy [2, 3]. However, the relationship between hemangioma and pregnancy is not clear. It is presumed that a characteristic feature (e.g. hormonal status) of pregnancy affects the formation of vaginal hemangiomas. This report focuses on not only the relationship between pregnancy and vaginal hemangioma, but also on the expressions of hormonal receptors in vaginal hemangiomas.

Materials and Methods

An asymptomatic 34-year-old woman (gravida 2, para 1) visited the antenatal clinic for routine follow-up at 18 weeks' gestation. She was treated with an episiotomy during the previous delivery. Clinical examination showed no apparent lesions in both the cervix and vagina. At 33 weeks' gestation, she complained of vaginal bleeding and a sensation of discomfort with walking and was referred to thus institution. Clinical examination showed a large reddish mass, approximately 5 cm in diameter, with bleeding, originating from the vaginal wall and protruding from the introitus (Figure 1A). Pelvic MRI showed a thickened vaginal mass with heterogeneous and a slightly high intensity on T2-weighted images (T2WI), the same intensity as soft tissue on T1-weighted images (T1WI) with further enhancement (Figure 1B). Hematoma, hemangioma, and malignant tumor were considered in the differential diagnosis. On excision, the vaginal mass was found to be a hemangioma. Seven weeks later, she gave birth safety to a baby (baby's weight: 3130 grams) through the vaginal tract. The patient provided her informed consent for the publication of this case.

The excised vaginal hemangioma was examined histopathologically and immunohistochemically. The expressions of hormonal receptors in the hemangioma were also examined. The following antibodies were used for immunohistochemical detection: anti-CD34 antibody (clone: My-10, anti-mouse monoclonal, 1:10), anti-erythroblast transformation-specific related gene (ERG) antibody (clone: ERP3864, anti-rabbit monoclonal, anti-vascular endothelial growth factor (VEGF) antibody (clone: A-20, anti-rabbit polyclonal, 1:200), anti-D2-40 antibody (clone: D2-40, anti-mouse monoclonal), anti-Ki-67 antibody (clone: MIB-1, anti-mouse monoclonal, 1:100), anti-estrogen receptor (ER) diluted antibody (clone: SP-1, anti-rabbit monoclonal), anti-progesterone receptor (PgR) diluted antibody (clone: 1E2, anti-rabbit monoclonal), and anti-hCG antibody (anti-rabbit polyclonal, 1:10000) in the vaginal hemangioma specimen and in another hemangioma (a skin hemangioma specimen in a non-pregnant case). Staining was performed using i-View DAB kit reagents and an auto-immunostainer, according to the manufacturer's instructions. Protein expression was assessed by two pathologists (T.Y. and J.T.). The expression of each was examined in vascular endothelial cells of the hemangioma or perivascular stromal cells around the hemangioma. Tissues from breast

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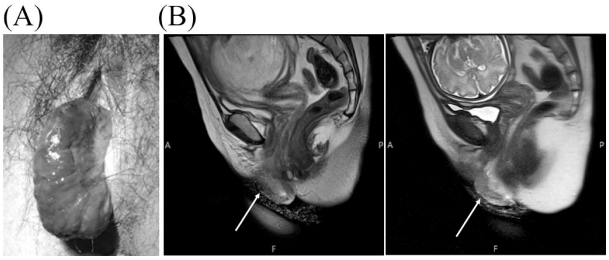

Figure 1. — (A) Gross findings. The reddish vaginal mass protrudes from the vaginal introitus. (B) Imaging findings. MRI shows the thickened and enhanced vaginal mass (arrow) of the perineum (left: T2-weighted image, right: enhanced T2-weighted image).

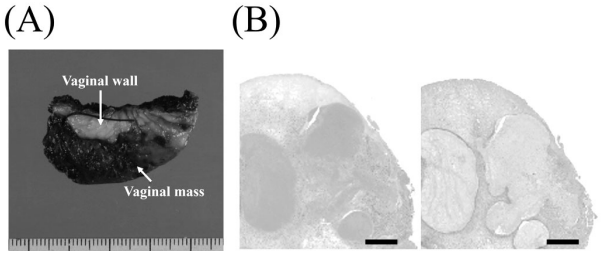

Figure 2. — (A) Resected specimen. A hematoma-like mass ($36\times18\times14$ mm^3) originates from the vaginal wall. The healthy vaginal wall is seen in the peripheral zone. (B) Histopathological findings. Proliferation of the various dilated vessels and hemorrhage in the stroma are identified in the polypoid lesion (left: HE stain, right: Elastic van Gieson stain). Bars, 1 mm.

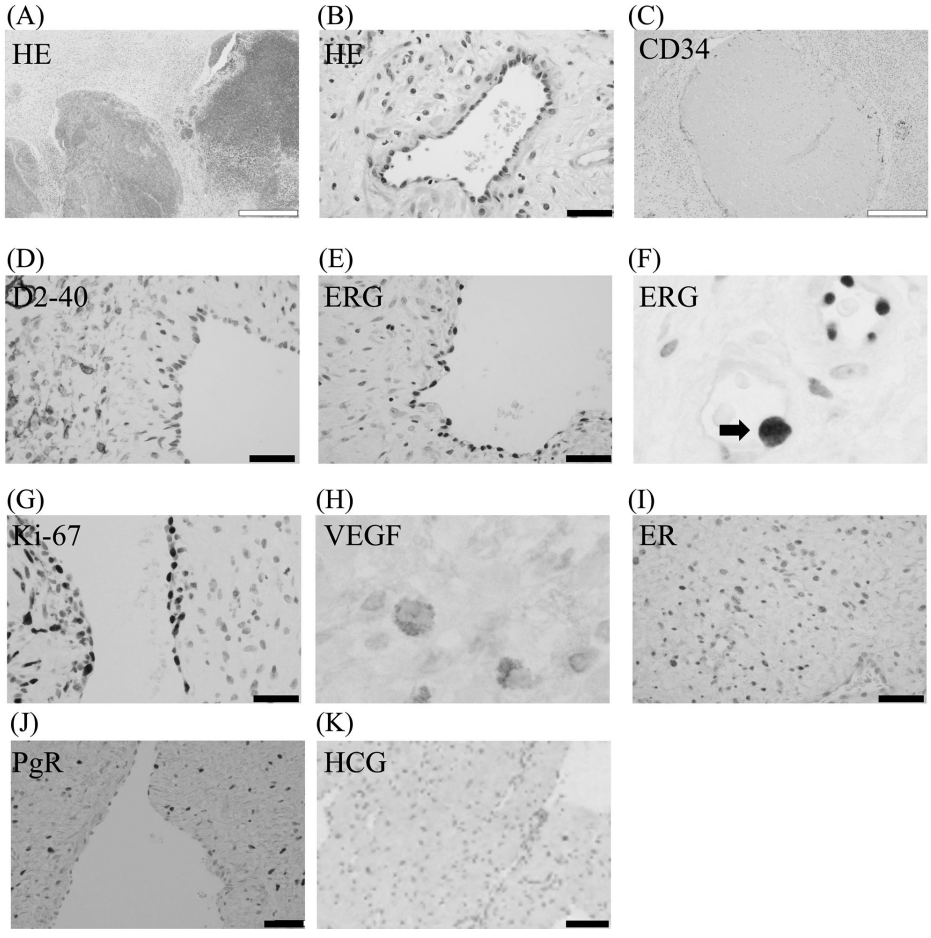

Figure 3. — Pathological and immunohistochemical findings. (A, B) HE stain. The congestion and hemorrhage are noted in the hemangioma and the increased endothelial cells are seen in the dilated vessels. (C-E, G) The increased vascular endothelial cells are positive for CD34, ERG, and Ki-67 but negative for D2-40. (F) A mitotic feature is seen in the ERG-positive endothelial cell (arrow). (H-K) The endothelial cells are negative for ER and PgR but the perivascular stromal cells are positive for ER, PgR, and VEGF but negative for hCG. White bars, 500 μm and black bars, 50 μm.

cancer (for ER and PgR), vascular endothelial cells (for ERG and CD34), lymphoid endothelial cells (for D2-40), placenta (for HCG), tonsil (for Ki-67), and colon cancer (for VEGF) were used as positive controls.

Previous reports of the two hemangiomas, both vaginal and cervical hemangiomas, were identified, and the relationship between hemangioma and pregnancy or oral contraceptive use, which contained both synthetic estrogen and progesterone, was examined.

Results

The vaginal mass was located superficially on the posterior wall mucosa. It could be clearly distinguished from the healthy vaginal wall and was completely resected (Figure 2A). Histopathological analysis showed a polypoid lesion with various dilated vessels which had increased endothe-

Table 1. — *Eight cases of vaginal hemangioma in the literature.*

	Age (years)	Relationship with pregnancy	Gestational age (weeks)	Delivery	Treatment
Rezvani [5]	32	+	37	Transvaginal	Excision
Wang [4]	61	-	-	-	Embolization
	45	+	NA	Transvaginal	Embolization
	31	+	Terminal	Transvaginal	Excision
Andola [6]	95	-	-	-	Excision
Celik [1]	24	+	32	Transvaginal	Excision
Yu [7]	30	+	40	Transvaginal	Embolization
Present case	34	+	33	Transvaginal	Excision

NA: not available.

lial cells which expressed CD34 and ERG but not D2-40 (Figures 2B, 3A-3E). Ki-67 expression was clearly found in the endothelial cells (Figure 3G) and a mitotic feature was also seen in the ERG-positive vascular endothelial cell (Figure 3F). The final diagnosis was not vaginal varix malformation but vaginal cavernous hemangioma.

Immunohistochemical analysis showed positive expressions of both ER and PgR in perivascular stromal cells around the hemangioma, but no expressions in vascular endothelial cells (Figures 3I, 3J). On the other hand, ER and PgR expressions were not found in the skin hemangioma (not shown). Additionally, hCG expression was not found but VEGF expression was noted in the perivascular stromal cells around the hemangioma. (Figures 3H, 3K).

Seven vaginal hemangiomas have been reported to date (Table 1) [1, 4-7]. Six cases (75%) were associated with pregnancy, in particular, late pregnancy, in addition to the present case. On the other hand, about 60 cervical hemangiomas have been reported in the literature [2, 8-29], and the relationships between hemangioma and pregnancy or oral contraceptive use were examined (Table 2).

Eight (32%) of 25 cervical hemangiomas and four (25%) of 16 cervical hemangiomas were found to be related to pregnancy or oral contraceptive use, respectively. All five cervical hemangioma cases that were related to pregnancy (excluding one case because the gestational weeks were not reported) were seen in late pregnancy (26-38 weeks), the same as in vaginal hemangioma cases.

Discussion

A cavernous hemangioma is a benign vascular tumor that rarely involves the female genital tract, especially the vagina [1]. In the female genital tract, a dilated vascular structure is sometime noted in the cases of hemangioma, vascular or lymphatic malformation and varix, but the gross findings of those diseases are similar to each other and a differential diagnosis is too difficult. The hemangioma is thought to gradually increasing over time and the pathological feature shows various dilated vessels with increased endothelial cells, which have tumorous potential. It is considered that hemangioma formation is due to injury or congenital malformation, but the pathogenesis remains unclear. In the present case, there were no conditions, such as trauma and infections, during pregnancy, and no obvious lesions of the vagina and cervix were seen until 18 gestational weeks. However, an episiotomy was performed at the previous delivery, at the same place as the vaginal hemangioma. Yu *et al.* recently also mentioned that the vaginal hemangioma in terminal pregnancy was observed at the previous episiotomy [7]. Therefore, the previous episiotomy may have affected the formation of the vaginal hemangioma in late pregnancy. Second, according to the previous studies, estrogen plays an important role in hemangioma formation in vivo [22], and estrogen promotes the proliferation of hemangioma in vitro [30, 31]. Reggiani Bonetti *et al.* reported the presence of estrogen receptors in both endothelial cells and stromal cells of cervical hemangiomas on immunohistochemical analysis [22]. Sun *et al.* previously reported that direct angiogenetic factors, VEGF, matrix metalloproteinase-9 (MMP-9), and nitric oxide (NO), or indirect angiogenetic factors, basic fibroblast growth factor (bFGF), insulin-like growth factor (IGF), and transforming growth factor (TGF), can contribute to the angiogenesis of hemangiomas through estrogen [31]. In addition, Duyka *et al.* mentioned that progesterone also promotes the expansion of vascular malformations [32]. In the present case, immunohistochemical analysis showed positive expressions of ER, PgR, and VEGF of the stromal tissue around the hemangioma in pregnancy. Taken together, estrogen and/or progesterone may promote angiogenesis of hemangiomas through the secretion of VEGF in pregnancy. Third, from the literature, six (75%) of eight vaginal hemangiomas and eight (32%) of 25 cervical hemangiomas were associated with pregnancy. Moreover, all vaginal and cervical hemangiomas related to pregnancy were diagnosed in late pregnancy (26-40 gestational weeks). Additionally, four (25%) of 16 cervical hemangiomas were found to be related to oral contraceptive use. Regarding hormonal status in pregnancy, both serum estradiol and progesterone are increased approximately 150 times and 12 times, respectively, in late pregnancy compared to non-pregnancy [33]. Outside of the female genital area, several hemangiomas were reported in nasal [34], oral

Table 2. — *Sixty cases of cervical hemangioma in the literature.*

	N	Age (years)	Relationship with pregnancy	Gestational age (weeks)	Contraceptive use
Ahern [8]	32	mean 32.7 (9-71)	NA	NA	NA
Mares [9]	1	6	-	-	NA
Pinheiro [10]	1	NA	+	NA	NA
Davis [11]	1	30	-	-	NA
Cherkis [12]	1	24	-	-	NA
Jackson [2]	1	22	+	38	-
Perty [13]	1	31	+	34	-
Padmanabhan [14]	1	34	-	-	+
Kondi-Pafiti [15]	2	NA	NA	NA	NA
Riggs [16]	1	33	+	Terminal	-
Shann [17]	1	28	-	-	NA
Baxi [18]	1	60	-	-	NA
Ozyer [19]	1	53	-	-	NA
Gupta [20]	1	38	-	-	NA
Tanaka [21]	1	39	+	26	-
Reggiani Bonetti [22]	3	33, 68, 48	-, -, -	-, -, -	+, -, -
Elkhateb [23]	1	25	+	34	-
Benjamin [24]	1	27	+	Terminal	-
Bharti [25]	1	28	-	-	NA
Mahapatra S [26]	1	27	+	34	-
Tran [27]	1	34	NA	NA	NA
Gada [28]	1	0 (4 months)	-	-	-
Busca [29]	4	42, 30, 32, 34	-, -, -, -	-, -, -, -	-, +, +, -

N: number, NA: not available.

[35], and spinal cord sites [36] during pregnancy. Cardoso *et al.* reported that over 50% of hemangiomatous lesions were found in the third trimester [35]. These reports were consistent with the present result that almost all vaginal hemangiomas were seen in late pregnancy.

In summary, the hormonal status in late pregnancy and previous episiotomy may affect the formation of vaginal hemangiomas. However, in the present study, it was not possible to elucidate the mechanisms of vaginal hemangioma formation in pregnancy because only one hemangioma case that occurred during pregnancy was analyzed, and VEGF was the only angiogenic marker used. Further studies are necessary to understand the mechanism of female genital hemangiomas in pregnancy.

Conclusion

The formation of hemangiomas in the female genital area is associated with late pregnancy and the hormonal status in pregnancy, and previous episiotomy may promote angiogenesis of hemangiomas.

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