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
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 endothel-
sidered that hemangioma formation is due to injury or con-
endothelial cells, which have tumorous potential. It is con-
logical feature shows various dilated vessels with increased
findings of those diseases are similar to each other and a
differential diagnosis is too difficult. The hemangioma is
vagina [1]. In the female genital tract, a dilated vascular
structure is sometime noted in the cases of hemangioma,
vaginal cavernous hemangioma.

Immunohistochemical analysis showed positive expres-
sions 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 heman-
gioma (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 heman-
giomas 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 hemangiomas 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 patho-
logical feature shows various dilated vessels with increased
endothelial cells, which have tumorous potential. It is con-
genital 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 gesta-
tional weeks. However, an episiotomy was performed at
the previous delivery, at the same place as the vaginal he-

mangioma, Yu et al. recently also mentioned that the vagi-
nal hemangioma in terminal pregnancy was observed at the
previous episiotomy [7]. Therefore, the previous epis-
iotomy may have affected the formation of the vaginal he-
mangioma in late pregnancy. Second, according to the
previous studies, estrogen plays an important role in he-
mangioma 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 heman-
giomas 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 an-
giogenesis 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 to-
gether, estrogen and/or progesterone may promote angi-
genesis 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 heman-
giomas 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 heman-
giomas were found to be related to oral contraceptive use.
Regarding hormonal status in pregnancy, both serum estra-
diol and progesterone are increased approximately 150
times and 12 times, respectively, in late pregnancy com-
pared to non-pregnancy [33]. Outside of the female genital
area, several hemangiomas were reported in nasal [34], oral

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

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Relationship with pregnancy</th>
<th>Gestational age (weeks)</th>
<th>Delivery</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rezvani [5]</td>
<td>32</td>
<td>+</td>
<td>37</td>
<td>Transvaginal</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>+</td>
<td>NA</td>
<td>Transvaginal</td>
</tr>
<tr>
<td></td>
<td>31</td>
<td>+</td>
<td>Terminal</td>
<td>Transvaginal</td>
</tr>
<tr>
<td>Andola [6]</td>
<td>95</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Celik [1]</td>
<td>24</td>
<td>+</td>
<td>32</td>
<td>Transvaginal</td>
</tr>
<tr>
<td>Yu [7]</td>
<td>30</td>
<td>+</td>
<td>40</td>
<td>Transvaginal</td>
</tr>
<tr>
<td>Present case</td>
<td>34</td>
<td>+</td>
<td>33</td>
<td>Transvaginal</td>
</tr>
</tbody>
</table>

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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References

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