

# Uterine Hemangioma

## A Rare Pathologic Entity

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• Uterine hemangioma is a rare benign tumor usually presenting with menorrhagia or pregnancy-associated complications. Although the current literature identifies fewer than 50 cases, we in our institution identified 5 similar cases among 3700 patients undergoing total hysterectomy from January 2006 to December 2010. Adenomyosis was the most common preoperative diagnosis among our patients. Vaginal examination, uterine curettage specimens, ultrasonography, and hystero-graphy are usually uninformative, and the definitive diagnosis relies on the final histologic examination. The differential diagnosis includes adenomatoid tumor, lymphangioma, and arteriovenous malformation. Uterine hemangiomas are classified into congenital and acquired. The former is believed to be associated with some hereditary diseases, while the latter is associated with both physical changes and hormone alteration, especially high estrogen level. The best treatment for hemangiomas is unclear. However, it is very important to obtain an accurate diagnosis to prevent overtreatment among reproductive-age women. The prognosis is excellent after hysterectomy.

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Uterine hemangioma was first described in 1897 and was an incidental discovery from an autopsy of a young woman who developed anemia and dyspnea and died 24 hours after delivering twins.<sup>1</sup> Its exact incidence still remains unclear owing to the extremely small number of case reports in the past century. Although the current literature identifies fewer than 50 cases, we found 5 similar cases among 3700 Taiwanese women who underwent total hysterectomies from January 2006 to December 2010.<sup>2</sup>

### CLINICAL FEATURES

Uterine hemangioma usually presents as menorrhagia or pregnancy-associated complications. We provide 7 reported cases in which the full texts were available, and detail the 5 cases treated at our hospital (Table 1).<sup>1-7</sup> Uterine hemangioma can be found in any age group, without predominance in any decade. The youngest patient was a 14-year-old girl who underwent hysterectomy for life-threatening bleeding.<sup>3</sup> The oldest patient was a 49-year-old woman who underwent hysterectomy for menorrhagia and dysmenorrhea. The clinical symptoms vary from asymptomatic to abdominal pain, excessive vaginal bleeding, anemia, and infertility to maternal and pregnancy-associated complications.<sup>1,5,7</sup>

Among all these cases, pregnant women are most commonly reported as having complications such as postpartum hemorrhage or disseminated intravascular coagulation (DIC). The hormone alternations that occur during pregnancy or the physical changes (increased blood volume and others) of the uterine structure during pregnancy or delivery may affect preexisting lesions and then trigger DIC.<sup>6</sup> The pathophysiology of DIC is generally presumed to be platelets trapped in the abnormally proliferating endothelium within the hemangioma.<sup>6</sup> Some authors believe this vascular lesion can also theoretically originate from angiomatous proliferation in a polypoid endometrial lesion that has persisted for a prolonged period. Increased blood flow provided by the endometrial hemangioma may prohibit normal cyclic shedding associated with the usual hormonal flux.<sup>1</sup>

Among pregnant women with hemangiomas, the courses of pregnancy were mostly uneventful in vaginal delivery, which is the preferred method of delivery.<sup>2</sup> However, in patients with hemangiomas who had undergone cesarean delivery, complications varied with no hemorrhage to severe hemorrhage. This indicates 2 possibilities: (1) the lesion could have increased in size in subsequent pregnancy or (2) the lesion was present but was localized away from the incision site.<sup>3</sup> Severe postpartum vaginal bleeding could have been due to the rupture of congested vessels or the inability of the dilated, thin-walled vessels to contract sufficiently.<sup>3,5</sup> Hypervascularity and angiomegaly, with a consequent increase in the vascular cross-sectional area, could cause amniotic fluid embolism.<sup>5</sup> Vaginal delivery is preferred owing to the possibility of incising the lesion during cesarean delivery. If cesarean delivery is required, a vertical incision should be performed.<sup>5</sup>

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**Table 1. Summary of Reported Cases and 5 Cases at Our Hospital**

Source, y	Age	GYN History	Location	Symptoms/Signs	Diagnosis	Treatment
Virk et al, <sup>3</sup> 2008	21	G3P2 (cesarean delivery)	Diffuse, endometrium and myometrium	Heavy bleeding after cesarean delivery	Diffuse cavernous hemangioma	Hysterectomy
Ali et al, <sup>4</sup> 2003	14	Nullipara	Polyp, endometrium	Menorrhagia with passage of blood clots and anemia	Capillary hemangioma	Oral contraceptive pills and low-dose steroids
Thanner et al, <sup>5</sup> 2001	26	G1	Diffuse, whole corpus	Atonic bleeding and amniotic fluid embolism after cesarean delivery	Diffuse cavernous hemangioma	Blood transfusion, prostaglandin F2 $\alpha$ , and oxytocin
Djunic et al, <sup>6</sup> 2009	33	Primigravida	Diffuse, left leg, vulva, uterus, and placenta	Increased D-dimer and low-grade DIC at 26 weeks of gestation, fetal demise	Diffuse cavernous hemangioma	LMWH, emergency cesarean delivery, and hysterectomy
Benjamin et al, <sup>2</sup> 2010	27	Nullipara	Diffuse, cervix and uterus	Torrential vaginal bleeding 11 weeks after cesarean delivery	Cavernous hemangioma	Hysterectomy
Malhotra et al, <sup>7</sup> 1995	14	Nullipara	Localized, endometrium and superficial myometrium of fundus	Menorrhagia and hemodynamically unstable	Cavernous hemangioma	Hysterectomy
Johnson et al, <sup>1</sup> 2005	39	G3P3	Nodule, endometrium	Menorrhagia	Capillary hemangioma	Hysterectomy
Our case 1	44	G3P3 (normal spontaneous delivery) Postpartum hemorrhage in P2	Diffuse, cervix and uterus	Menorrhagia	Diffuse cavernous hemangioma	Hysterectomy
Our case 2	49	G2P2 (normal spontaneous delivery)	Diffuse, cervix and uterus	Anemia, menorrhagia, and dysmenorrhea	Diffuse cavernous hemangioma	Hysterectomy
Our case 3	44	G3P3 (normal spontaneous delivery)	Diffuse, cervix and uterus	Suprapubic heavy sensation and menorrhagia	Diffuse cavernous hemangioma and leiomyoma	Hysterectomy
Our case 4	41	G2P2 (normal spontaneous delivery)	Diffuse, cervix and uterus	Dysmenorrhea	Diffuse cavernous hemangioma and leiomyoma	Hysterectomy
Our case 5	43	G3P3 (normal spontaneous delivery)	Diffuse, cervix and uterus	Prolonged menstrual period with anemia	Diffuse cavernous hemangioma	Hysterectomy

Abbreviations: DIC, disseminated intravascular coagulation; GP, gravida/para; GYN, gynecologic; LMWH, low-molecular-weight heparin.

## DIAGNOSIS

The definitive diagnosis relies on the final histologic examination. Several reports have shown that vaginal examination, uterine curettage specimens, ultrasonography, and hystero-graphy are usually uninformative.<sup>7</sup> Nonetheless, the uterus may rarely appear pulsatile on examination, ultrasonography, or fluoroscopy.<sup>7</sup> Pelvic angiography or computed tomography could confirm the vascular nature of the lesion if there were clinical suspicion for this abnormality in cases refractory to hormonal therapy and curettage.<sup>7</sup> Magnetic resonance imaging could also serve as an additional imaging modality for diagnosis.<sup>3</sup> A sonographically guided biopsy could be helpful for diagnosis and could help avoid unnecessary total hysterectomies, especially for reproductive-age women. Adenomyosis was the most common preoperative diagnosis among our patients owing to the clinical symptoms of dysmenorrhea and menorrhagia, without obvious mass-like lesions in ultra-sonography. Our experience suggests that determining the correct diagnosis before surgery is very difficult.

## GROSS PATHOLOGY

Uterine hemangioma lesions show some dilated vascular spaces with adjacent brownish-color changes in

myometrium (Figure 1). Both localized and diffuse patterns are reported. It is possible that some lesions grow gradually over the years and come to involve the whole uterus.<sup>3</sup> We saw similar but localized, small-area vascular changes with some of our patients. The most commonly involved uterine structure is the myometrium of the uterine corpus, while the most common pattern of distribution is the diffuse type.<sup>1</sup> Hemangioma can also involve the cervix, serosa, endometrium, placenta, vulva, vagina, and ovaries.<sup>2,6,8</sup>

## HISTOPATHOLOGY

The term *hemangioma* defines a benign, nonreactive process with increased numbers of normal or abnormally appearing vessels, indicating that many of these lesions represent tissue malformations rather than true tumors.<sup>9</sup> Microscopically, uterine hemangioma shows a picture of irregularly shaped cavernous vascular spaces infiltrating between the myometrial fascicles (Figure 2). The large vascular spaces are walled by flat endothelial cells and distended by blood. No centrally placed larger vessels or cell atypia is seen.

## IMMUNOHISTOCHEMISTRY

The cells lining the vascular spaces are immunoreactive for endothelial markers including von Willebrand factor,



**Figure 1.** Gross examination of uterine hemangioma. The serosa over the uterus is smooth and glistening. The outer one-fourth to one-third of the myometrium and cervix shows diffusely dilated spaces with adjacent brownish-color changes in myometrium. A huge leiomyoma is seen in the fundus.

CD31 (Figure 3), and CD34. In contrast, the mesothelial markers including calretinin (Figure 4) and cytokeratin yield negative results. The direct influence of hormones is not confirmed via immunohistochemical studies, as no staining with either estrogen receptor (Figure 4) or progesterone receptor is seen for cells lining the vascular spaces. Weiss et al<sup>9</sup> have suggested that different immunophenotypic profiles may also be used to classify a hemangioma into different phases. During the early proliferative phase (0–12 months), the tumor cells are immunoreactive for proliferating cell nuclear antigen, vascular endothelial growth factor, and type IV collagenase. Proliferating cell nuclear antigen and vascular endothelial growth factor can stain both endothelium and pericytes, while type IV collagenase stains only the endothelium.<sup>9</sup> In contrast, during the involuting phase (1–5 years), these substances diminish, while the tissue inhibitors of metalloproteinases and antiangiogenic factors dramatically increase.<sup>9</sup> Traditional vascular markers such as CD31, von Willebrand factor, and smooth muscle actin (a pericyte marker) are present in both the proliferative and involuting phases, but are lost in the fully involuted lesions.<sup>9</sup> The involuting or involuted phase of hemangioma in our patients was also demonstrated by weak cytoplasmic or negative staining for v-ski sarcoma viral oncogene homolog (avian) (SKI, Figure 5).<sup>10</sup>

### DIFFERENTIAL DIAGNOSIS

Like hemangiomas, vascular dilatation can also be found in other benign lesions, such as adenomatoid tumor, lymphangioma, and arteriovenous malformation. The summary of the differential diagnosis is listed in Table 2.<sup>9</sup>

An adenomatoid tumor is a benign mesothelial neoplasm, which usually presents as a solitary or multinodular, small, indurated mass or swelling located at the uterine cornu.<sup>9</sup> The characteristic microscopic findings are irregularly arranged, dilated tubular channels and glandlike spaces lined by flattened or solid nests of cells.<sup>9</sup> The mesothelial cells are immunopositive for cytokeratins, calretinin, thrombomodulin, D2-40, anti-Wilms tumor 1, HMBE-1, CA 125, and cytokeratin 5/6.<sup>9</sup> The immunoprofiles of our patients were

negative for calretinin and cytokeratin, and the tumor location was solely in the upper cervix and corpus, with diffuse pattern of distribution. Therefore, adenomatoid tumor was unlikely.

With lymphangioma, as with hemangioma, it is often difficult to tell whether or not this entity is a true neoplasm, hamartoma, or lymphangiectasia.<sup>9</sup> The small lymphatic channels are similar to capillaries. Grossly, clusters of thin-walled vesicles filled with clear fluid are seen.<sup>9</sup> The lack of erythrocytes in the lumen distinguishes lymphatic channels from capillaries.<sup>9</sup> The lymphatic channels usually lack actin-positive pericytes, except for large channels.<sup>9</sup> Owing to marked distension of vascular channels by erythrocytes in our patients, this entity was excluded.

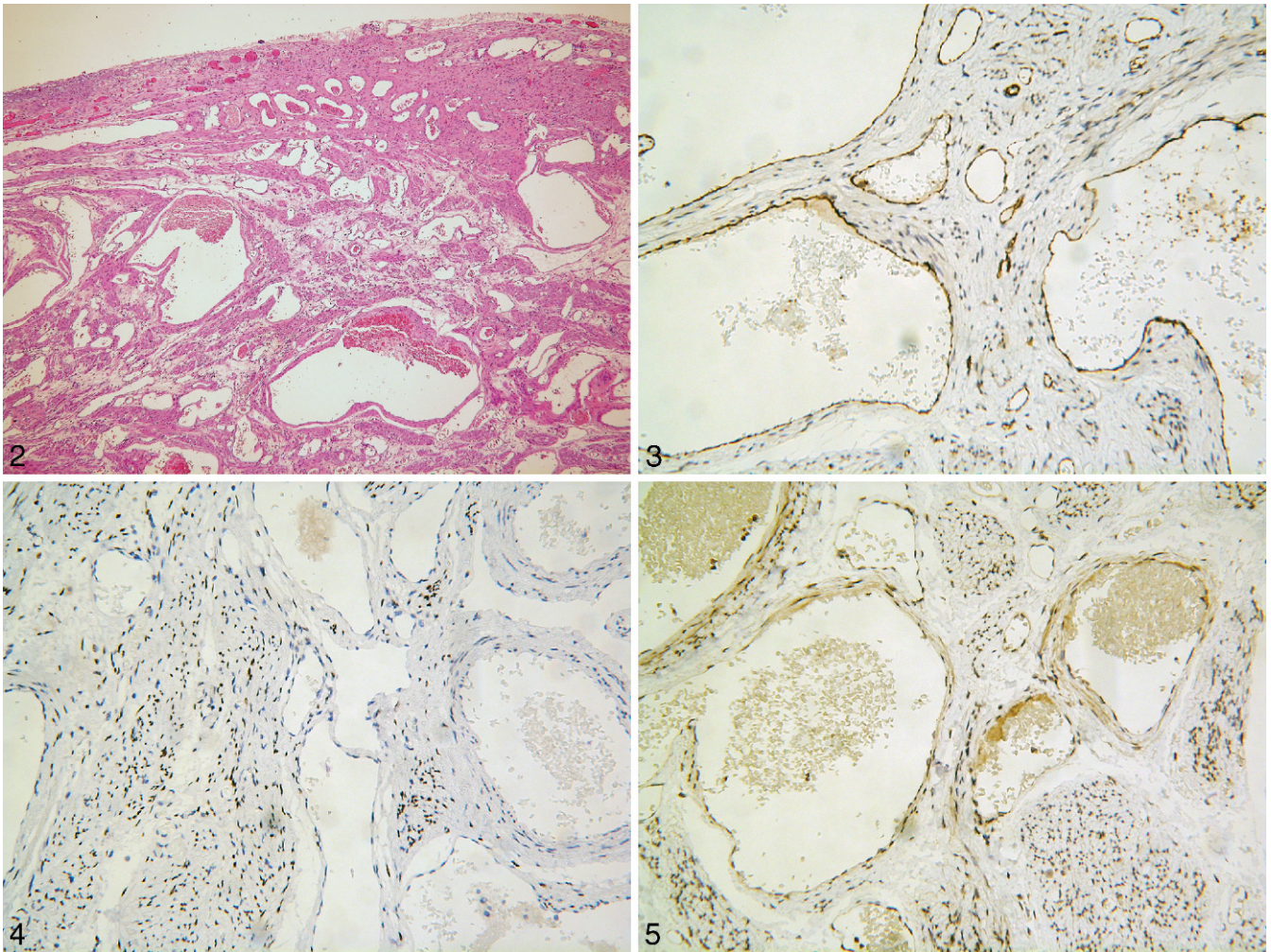
Arteriovenous malformation is composed of a mass of arterial and venous vessels of various sizes, with fistula formation between them.<sup>9</sup> Gradually, the malformation replaces the normal myometrium.<sup>4</sup> Our patients had irregularly shaped cavernous vascular spaces diffusely infiltrating between the myometrial fascicles. Therefore, the diagnosis of arteriovenous malformation was eliminated.

### PATHOGENESIS

The origin of uterine hemangioma cells possibly represents pluripotent, embryogenic, mesodermal cells within the uterus.<sup>1</sup> Uterine hemangioma is classified into congenital and acquired. Congenital hemangioma is believed to be associated with hereditary diseases, including Klippel-Trenaunay syndrome, hereditary hemorrhagic telangiectasia, tuberous sclerosis, blue rubber bleb nevus syndrome, Maffucci syndrome, and Kasabach-Merritt syndrome.<sup>1,9</sup> The endothelium is usually in the proliferative phase. Acquired hemangioma is associated with both physical changes and hormone alterations<sup>6,9</sup> (Table 3). Most of the reported cases are classified as acquired hemangiomas, and the endothelia are usually in the involuting or involuted phase.

Different growth phases of hemangiomas are classified according to the morphology of the endothelium and the intensity of SKI staining. SKI acts as a repressor of the transforming growth factor pathway as well as a promoter of the WNT/ $\beta$ -catenin signaling pathway.<sup>10</sup> The SKI oncogene protein is upregulated by hemangiomas, leading to uncontrolled cellular proliferation and transformation.<sup>10</sup> In the proliferative phase, most of the endothelial cells are immature and plumper, and SKI localized to the nucleus of endothelial cells shows a perinuclear pattern.<sup>10</sup> In contrast, in the involuted phase, the mature endothelial cells show only mild cytoplasmic or even negative staining for SKI.<sup>10</sup>

Many theories propose that hormones play a crucial role in development of hemangiomas, although their direct influence was not confirmed via immunohistochemical studies of estrogen receptor and progesterone receptor in our patients. Sun et al<sup>11</sup> proposed a model for pathogenesis based on the clinical and laboratory evidence that estrogen influences the vasculogenesis and angiogenesis of hemangiomas via an indirect pathway of angiogenic factors.<sup>11</sup> Estrogen induces an increase in endothelial progenitor cells (EPCs) and angiogenic factors such as matrix metalloproteinase 9, vascular endothelial growth factor, nitric oxide, and other related factors.<sup>11</sup> These EPCs in the bone marrow move to the circulation under the effect of matrix metalloproteinase 9.<sup>11</sup> The circulating EPCs “home in” on angiogenic areas and then attach to the endothelia of the vessels in the capillary bed,



**Figure 2.** Microscopically, the subserosal region of the myometrium shows irregularly shaped cavernous vascular spaces infiltrating between the myometrial fascicles and located predominantly in the outer portion of the myometrium. The large vascular spaces are walled by flat endothelial cells and distended by blood. No endothelial cell atypia is seen (hematoxylin-eosin, original magnification  $\times 20$ ).

**Figure 3.** The endothelial cells are immunoreactive for CD31 (Novocastra Laboratories Ltd, Newcastle upon Tyne, United Kingdom) (original magnification  $\times 200$ ).

**Figure 4.** Results of the immunohistochemical study of endothelial cells are negative for estrogen receptor (ER; Novocastra Laboratories Ltd, Newcastle upon Tyne, United Kingdom). By contrast, the adjacent myometrial cells are immunoreactive for ER (original magnification  $\times 200$ ).

**Figure 5.** The involuted phase of hemangioma is demonstrated by weak cytoplasmic staining for SKI (sarcoma viral oncogene; Abcam, Cambridge, Massachusetts) (original magnification  $\times 200$ ).

**Table 2. Differential Diagnosis of Uterine Hemangioma**

Characteristic	Hemangioma	Adenomatoid Tumor	Lymphangioma	Arteriovenous Malformation
Gross pathology	Dilated vascular spaces with adjacent brownish-color changes	Small indurated mass or swelling at uterine cornu	Clusters of thin-walled vesicles filled with clear fluid	The malformation gradually replaces the normal myometrium
Histopathology	Dilated vascular channels lined by a single flat layer of endothelium, contain blood cells	Irregularly arranged, dilated tubular channels and glandlike spaces lined by flattened or solid nests of cells	Thin-walled vessels not containing blood cells	A proliferation of arterial and venous vessels of various sizes with fistula formation between them
IHC				
vWF/CD31/CD34	+	-	+	+
Calretinin	-	+	-	-
Cytokeratin	-	+	-	-

Abbreviations: IHC, immunohistochemistry; vWF, von Willebrand factor.

**Table 3. Etiology of Acquired Hemangioma**

Physical Changes	Hormone Alteration (Especially High Estrogen Level)
1. Tissue injury 2. Hypoxia 3. Increased blood volume during pregnancy 4. Previous pelvic surgery 5. Endometrial curettage	1. Menarche 2. Pregnancy 3. Trophoblastic disease 4. Endometrial carcinoma 5. Maternal ingestion of diethylstilbestrol

acting as potent proliferation and migration factors for endothelial cells, thus resulting in the formation of hemangiomas.<sup>11</sup>

**CURRENT TREATMENT AND PROGNOSIS**

The best treatment for hemangiomas remains unclear. Some authors describe conservative treatments such as carbon dioxide laser excision, knife excision, cryotherapy, radiotherapy, electrocauterization, internal artery ligation, uterine artery embolization, local excision, conization, and laser ablation.<sup>2,3,12</sup> If hemangiomas are refractory to conservative treatments, hysterectomy may be considered.<sup>2</sup> Radiotherapy has been suggested as a possible treatment but it would affect ovarian function as well.<sup>2</sup> For reproductive-age women, it is very important that the diagnosis of uterine hemangioma be correct. Conservative treatment may be offered as a first-choice option before total hysterectomy. Thus, it is also very important for pathologists to be aware of the diagnosis of uterine hemangioma, not only because of its possible life-threatening complications, but also because of the need for individualized treatments to avoid further complications or overtreatment.<sup>12</sup>

All patients listed in Table 1 had uneventful recoveries after conservative treatments or surgical resections.

**References**

1. Johnson C, Reid-Nicholson M, Deligdisch L, Grinblat S, Natarajan S. Capillary hemangioma of the endometrium: a case report and review of the literature. *Arch Pathol Lab Med.* 2005;129(10):1326–1329.
2. Benjamin MA, Yaakub H, Telesinghe PU, Kafeel G. A rare case of abnormal uterine bleeding caused by cavernous hemangioma: a case report. *J Med Case Reports.* 2010;4(1):136.
3. Virk RK, Zhong J, Lu D. Diffuse cavernous hemangioma of the uterus in a pregnant woman: report of a rare case and review of literature. *Arch Gynecol Obstet.* 2008;279(4):603–605.
4. Ali SS, Muzaffar S, Kayani N, Setna F. Capillary haemangioma of the uterus: a rare cause of menorrhagia. *Aust N Z J Obstet Gynaecol.* 2003;43(1):85–86.
5. Thanner F, Suetterlin M, Kenn W, et al. Pregnancy-associated diffuse cavernous hemangioma of the uterus. *Acta Obstet Gynecol Scand.* 2001;80(12):1150–1151.
6. Djunic I, Elezovic I, Ljubic A, Markovic O, Tomin D, Tadic J. Diffuse cavernous hemangioma of the left leg, vulva, uterus, and placenta of a pregnant woman. *Int J Gynaecol Obstet.* 2009;107(3):250–251.
7. Malhotra S, Sehgal A, Nijhawan R. Cavernous hemangioma of the uterus. *Int J Gynaecol Obstet.* 1995;51(2):159–160.
8. Gerbie AB, Hirsch MR, Greene RR. Vascular tumors of the female genital tract. *Obstet Gynecol.* 1955;6(5):499–507.
9. Weiss SW, Goldblum JR, Enzinger FM. *Enzinger and Weiss's Soft Tissue Tumors.* St Louis, MO: Mosby; 2001.
10. O TM, Tan M, Tarango M, et al. Differential expression of SKI oncogene protein in hemangiomas. *Otolaryngol Head Neck Surg.* 2009;141(2):213–218.
11. Sun ZY, Yang L, Yi CG, et al. Possibilities and potential roles of estrogen in the pathogenesis of proliferation hemangiomas formation. *Med Hypotheses.* 2008;71(2):286–292.
12. Gupta R, Singh S, Nigam S, Khurana N. Benign vascular tumors of female genital tract. *Int J Gynecol Cancer.* 2006;16(3):1195–1200.