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Original Article

Characterization of clinicopathological features of tubal cavernous hemangioma

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Abstract: Hemangioma is a benign tumor of vascular origin. Although hemangiomas are observed quite frequently, particularly in the skin and soft tissue, the rarity with which they are encountered in the fallopian tube makes the present study worth reporting in the literature. Cavernous hemangiomas of the fallopian tube are rare benign tumors that have been documented to date as isolated case reports only. Here we demonstrate a rare case of incidentally detected tubal cavernous hemangioma in a 49-year-old woman who underwent hysterectomy with right salpingo-oophorectomy for high-grade squamous intraepithelial lesion of the uterine cervix and an endometriotic cyst of the right ovary. Histopathological examination of a thickened tubal segment revealed a 1.2-cm relatively well-circumscribed nodular lesion consisting of dilated cavernous spaces filled with red blood cells. The majority of the vessels were thin-walled. The lining endothelium had bland-looking nuclei without cytologic atypia or mitotic figures. The tubal epithelium showed no pathological abnormalities. Strong and uniform CD31 and CD34 immunoreactivity in the lining endothelial cells confirmed the diagnosis of a benign vascular tumor. We also conducted a thorough review of the relevant literature with respect to the epidemiology, clinical manifestation, pathology, immunophenotype, and treatment options for hemangiomas arising in the fallopian tube.

Keywords: Hemangioma, cavernous hemangioma, fallopian tube

Introduction

Hemangioma is a benign vascular tumor originating from the endothelial cells that line the interior surface of blood vessels [1, 2]. Clinically, hemangiomas can manifest with bluish skin discoloration and a history of size fluctuation [2, 3]. Pain may occur after exercise owing to shunting of blood flow away from the surrounding tissue into the hemangioma [2, 3]. On imaging, hemangiomas can be seen to contain serpentine vessels, fat, smooth muscle, hemosiderin, and phlebolith [2, 3]. Histologically, hemangiomas are classified based on the predominant vascular channel type: capillary, cavernous, arteriovenous, and venous [4, 5]. Cavernous hemangiomas are found in the skin as well as in the liver, kidneys, breast, brain, bone, and skeletal muscle. It is morphologically characterized by cavern-shaped vascular spaces that are much wider than those of capillary hemangioma and are lined with bland endothelial cells.

Hemangioma occurs uncommonly in the female genital organs with the exception of the vulva. Fallopian tube hemangiomas are rare neoplasms; only a few cases have been reported to date in the English literature [6-13]. Here we describe an unusual case of cavernous hemangioma of the fallopian tube that was incidentally detected in a postmenopausal woman and emphasize its histopathological and immunohistochemical features. We also thoroughly review the clinicopathological features of previously reported cases of fallopian tube hemangioma.

Patient and methods

Case presentation

A 49-year-old woman was referred from an outside hospital with an abnormal cervical punch biopsy result of high-grade squamous intraepithelial lesion (HSIL; cervical intraepithelial neo-

Table 1. Antibodies used for immunohistochemical staining

Antibody	Source	Clone	Dilution
CK7	Dako, Agilent Technologies, Inc., Carpinteria, CA, USA	OV-TL 12/30	1:100
CD31	Dako, Agilent Technologies, Inc., Carpinteria, CA, USA	JC70A	1:40
CD34	Dako, Agilent Technologies, Inc., Carpinteria, CA, USA	QBEnd 10	1:50
D2-40	Dako, Agilent Technologies, Inc., Carpinteria, CA, USA	D2-40	1:50
Desmin	Dako, Agilent Technologies, Inc., Carpinteria, CA, USA	D33	1:500
Ki-67	Dako, Agilent Technologies, Inc., Carpinteria, CA, USA	MIB-1	1:150

CK7: cytokeratin 7.

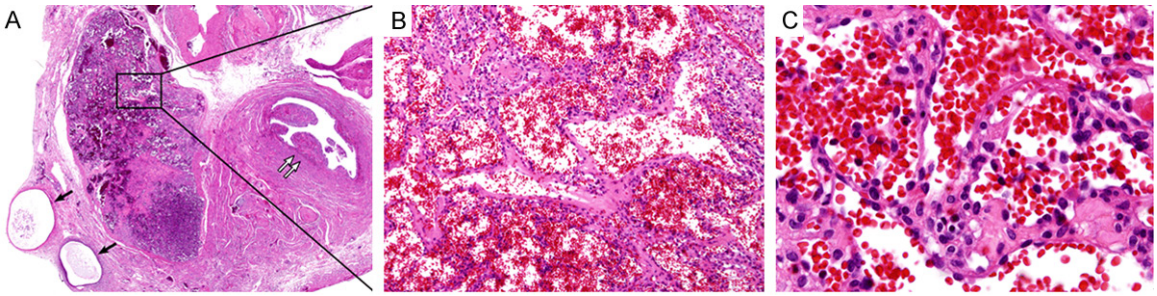

Figure 1. Histopathological findings of tubal cavernous hemangioma. A. There is a well-circumscribed mass located adjacent to the fallopian tube. Double white arrows indicate the tubal mucosa. Two black arrows indicate endometriotic foci in the mesosalpinx (left lower corner). B. Note the multiple, dilated vascular channels. Each channel is filled with red blood cells. C. The vascular spaces are lined with a single layer of benign endothelial cells, which have bland-looking nuclei and scant cytoplasm.

plasia 2). On physical examination, she was alert, cooperative, and in no apparent distress. She had no symptoms or signs of disease. She underwent cervical conization followed by hysterectomy with right salpingo-oophorectomy and pelvic peritoneal biopsy. The pathological diagnosis of the conization specimen was HSIL (CIN 2) with endocervical glandular extension. A histopathological examination of the resected specimens, including the uterus, right adnexa, and pelvic peritoneum, was performed.

Histopathological examination

The resected specimens were fixed in 10% neutral-buffered formalin and embedded in paraffin blocks. From each formalin-fixed, paraffin-embedded (FFPE) block, 4-μm sections were cut and stained with hematoxylin and eosin, and prepared for immunohistochemical staining. All slides were examined under routine light microscopy by two independent pathologists.

Immunohistochemistry

FFPE sections were deparaffinized and rehydrated with a xylene and alcohol solution. Immunohistochemical staining used the Ventana Benchmark XT automated staining system (Ventana Medical Systems, Inc., Tucson, AZ, USA) or Dako Omnis (Dako, Agilent Technologies, Inc., Carpinteria, CA, USA) according to the manufacturer's instructions. Antigen retrieval used Cell Conditioning Solution (CC1; Ventana Medical Systems, Inc.) or EnVision FLEX Target Retrieval Solution, High pH (Dako, Agilent Technologies, Inc.). Sections were incubated with primary antibodies (**Table 1**). After chromogenic visualization using ultraView Universal DAB Detection Kit (Ventana Medical Systems, Inc.) or EnVision FLEX/HRP (Dako, Agilent Technologies, Inc.), slides were counterstained with hematoxylin and coverslipped. Appropriate positive and negative controls were stained concurrently to validate staining.

Literature review

The Medline database was thoroughly searched using the PubMed retrieval service. Searches were performed using the key words "fallopian tube", "salpinx", "hemangioma", and "cavernous hemangioma". Eight cases of cavernous hemangioma of the fallopian tube were found.

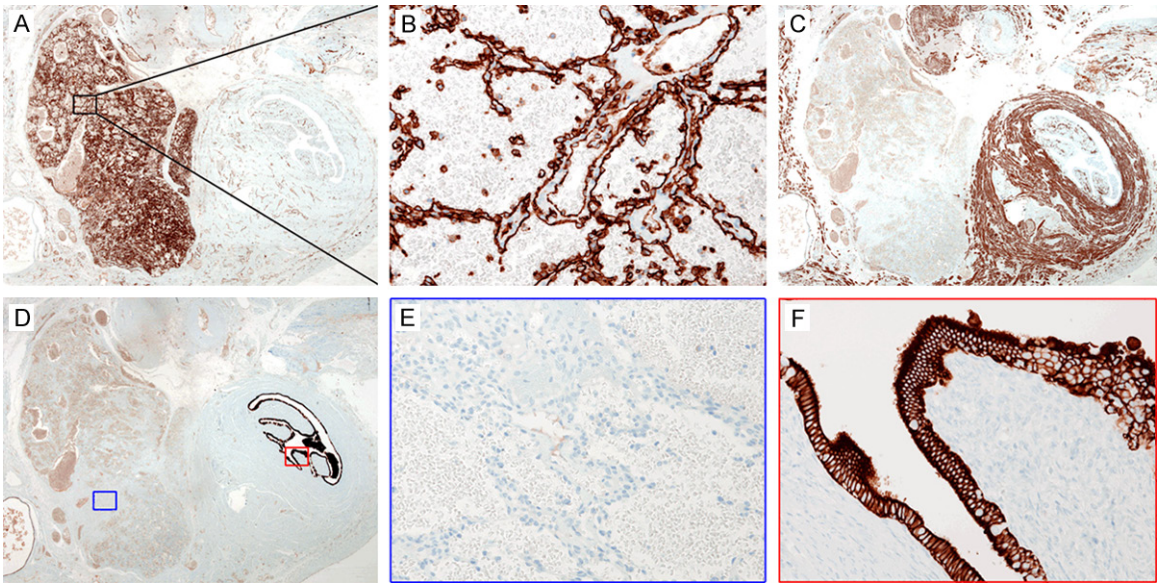

Figure 2. Immunohistochemical findings of tubal cavernous hemangioma. A. CD31 immunostaining highlights the tumor, but not the tubal mucosa and smooth muscle layer. B. A high-power view of image A demonstrates dilated, variable-sized, thin-walled vascular spaces. Each tumor cell reveals membranous CD31 immunoreactivity. C. Desmin immunostaining highlights the tubal smooth muscle layer, but not the tumor. D. The tubal mucosa strongly expresses CK7. E. A high-power view of the blue square in image D demonstrates the absence of CK7 expression in the tumor cells. F. A high-power view of the red square in image D demonstrates strong and uniform immunoreactivity for CK7 in the tubal epithelium.

We reviewed the clinical and pathological features of the previous cases in addition to the current case.

Results

On macroscopic examination, the uterine cervix and endometrium showed no remarkable lesions. The right ovary displayed a benign-appearing, thin-walled cystic lesion filled with chocolate-colored old blood, consistent with an endometriotic cyst. The right fallopian tube had a thickened segment in the ampulla. The fimbria was unremarkable. The cut surfaces of the ampullary mass were hemorrhagic with an area that was spongy and irregular and measured 1.2×0.6 cm. Microscopic examination revealed an obvious nodular proliferation of vascular channels (**Figure 1A**) consisting of dilated and cavernous blood-filled spaces (**Figure 1B**). These vascular spaces were lined with a single layer of endothelial cells (**Figure 1C**). The individual tumor cells had flattened nuclei and scant cytoplasm and no cytologic atypia or mitotic figures. No coagulative necrosis was identified. The tubal epithelium revealed no pathological abnormality. The mesosalpinx and pelvic peritoneum showed a few microscopic foci of endometriosis.

Immunohistochemical staining for CD31, CD34, cytokeratin 7 (CK7), D2-40, desmin, and Ki-67 was performed. Strong CD31 (**Figure 2A**) and CD34 immunoreactivity in the lining endothelium confirmed the diagnosis of a benign tumor of vascular origin. The individual tumor cells exhibited uniform membranous expression for both vascular endothelial markers (**Figure 2B**). Desmin immunostaining highlighted the tubal smooth muscle coat (**Figure 2C**), but not the tumor cells. The tubal mucosa strongly expressed CK7 (**Figure 2D**). The tumor cells were negative for desmin, D2-40, and CK7 (**Figure 2E**), whereas the epithelial cells lining the tubal lumen were highlighted by CK7 (**Figure 2F**). The Ki-67 labeling index was very low (< 1%) in the tumor tissue.

The patient made an uneventful postoperative recovery and was discharged from the hospital 6 days after the operation.

Discussion

The pelvic vascular system may include various kinds of abnormal vessels in addition to normal arterial and venous structures. Abnormally dilated vessels and collateral vessel development may occur as a result of increased blood

Table 2. Clinical features of tubal cavernous hemangioma

Case	Author (year)	Age	Side	Symptom	Imaging finding	Clinical impression	Associated disease	Management
1	Ragins et al. (1947) [6]	28	Left	Lower abdominal pain and dysmenorrhea	None	Tubo-ovarian disease	None	LSO
2	Talerman (1969) [7]	23	Left	Dysmenorrhea	None	NM (incidental)	Mental deficiency	LSO+H
3	Ebrahimi et al. (1973) [8]	66	Left	Vaginal discharge	None	NM (incidental)	Endometrial cancer	BSO+H
4	Patel et al. (1973) [9]	30	Right	Right lower quadrant pain	None	Acute appendicitis	Hemoperitoneum	RS+A
5	Joglekar et al.(1979) [10]	24	Left	Lower abdominal pain	None	Ovarian cyst torsion	Hemoperitoneum	LS
6	Atere-Roberts et al. (2010) [11]	14	Right	Right lower quadrant pain	None	Acute appendicitis	Hemoperitoneum	RS+A
7	Wojnar et al. (2010) [12]	69	Left	None	None	NM (incidental)	Endometrial cancer	BSO+H
8	Deb et al. (2014) [13]	50	Left	Dysmenorrhea	A pelvic cystic lesion	NM	Adenomyosis	BSO+H
9	Kim et al. (2016) [The present study]	49	Right	None	None	NM (incidental)	Cervical HSIL and tubo-ovarian endometriosis	RSO+H

NM: not mentioned; HSIL: high-grade squamous intraepithelial lesion; LSO: left salpingo-oophorectomy; H: hysterectomy; BSO: bilateral salpingo-oophorectomy; RS: right salpingectomy; A: appendectomy; LS: left salpingectomy; RSO: right salpingo-oophorectomy.

Table 3. Pathological features of tubal cavernous hemangioma

Case	Macroscopic finding	Location	Size	Microscopic finding	Immunostaining result
1	A polypoid, dark purple-to-red mass filling the entire lumen	Fimbria	1.5 cm	Cavernous hemangioma	None
2	A small, round, red-to-brown lesion bulging into the lumen	Middle-third	0.5 cm	Cavernous hemangioma	None
3	A slight bulge	Mid-portion	0.8 cm	Cavernous hemangioma	None
4	An encapsulated, slightly transparent, spongy mass with blood-filled cystic spaces	Fimbria	3.5 cm	Cavernous hemangioma	None
5	A dilated lumen filled with blood clot	Fimbria	2.0 cm	Cavernous hemangioma	None
6	A dilated tubal segment with a hemorrhagic mass	NM	3.5 cm	Cavernous hemangioma	None
7	NM	NM	0.3 cm	Cavernous hemangioma	CD34 (P), CD31 (P), EMA (N), LYVE (N)
8	A mixed solid and cystic nodule with congestion	Ampulla	3.0 cm	Cavernous hemangioma	CD34 (P)
9	A thickened tubal segment with blood-filled cystic spaces	Ampulla	1.2 cm	Cavernous hemangioma	CD34 (P), CD31 (P), D2-40 (N)

NM: not mentioned; P: positive; N: negative; EMA: epithelial membrane antigen; LYVE: lymphatic vessel endothelial hyaluronan receptor.

pressure, stenosis, or abnormal positioning (such as stretching, compression, torsion, and kinking). The development of vascular lesions or pelvic neoplasms can also be involved in the vascular dilatation. Among these factors that may be involved in the production of dilated and cavernous blood vessels, one can eliminate the possibility of torsion or trauma in our case since the resected tissue's viability was apparent. The possibility of an association with a neoplastic lesion can also be excluded. Inflammatory changes characterized by the formation of granulation tissue with increased capillarization did not play a role in the tumor reported here. In our case, the folds were well preserved and the supporting stroma and muscular layer showed no morphological evidence of inflammatory infiltrate. In two previous case reports, fallopian tube hemangiomas were associated with adenocarcinoma of the endometrium [8, 12]. Ebrahimi and Okajaki [8] stated that hemangioma might be related to the female sex hormone and suggested that a hemangioma might first develop or rapidly increase in size at the onset of menstruation or in pregnancy because the numbers, weight, and volume of blood vessels increase during pregnancy [7]. They also mentioned that the co-existence of fallopian tube hemangioma and endometrial adenocarcinoma in their patient may support the hormonal theory of hemangioma development. Similarly, Atere-Roberts and colleagues [11] suggested that estrogen might play a part in hemangioma growth because their patient presented within months of menarche. In addition, based on the history of preoperative radiation therapy, Ebrahimi and Okajaki [8] raised the possibility that radiation was one of the incriminating factors in the development of tubal hemangioma. However, in seven of the nine patients examined here, no association was found with endometrial adenocarcinoma or other estrogen-related neoplasms, and two of the seven patients were menopausal women. Moreover, the seven patients did not receive radiation therapy. Therefore, it is difficult to conclude that female sex hormone or prior radiation therapy is involved in the development of hemangioma occurring in the fallopian tube. Thus, the pathogenesis of tubal hemangioma remains unknown.

The lesion described in this case was incidentally identified and produced no specific signs or symptoms due to its size and location. However, the histopathological features of such lesions, if as a rule unequivocal, require differentiation from lymphangioma, vascular leiomyoma, mesothelioma, and adenomatoid tumor. Immunohistochemical staining can help distinguish hemangiomas from histopathological mimics. The hemangioma manifests positive reactions for vascular endothelial markers CD31 and CD34. However, it does not react with lymphatic vessel endothelial hyaluronan receptor-1, which distinguishes it from lymphangioma; epithelial membrane antigen, which excludes epithelial origin of the tumor; and Ki-67, which excludes the tumor's proliferative nature or malignant transformation. In our case, CD31 expression of was documented, which, in the absence of Ki-67 expression, unequivocally confirmed the diagnosis of a benign tumor of vascular origin.

The clinical and pathological features of tubal cavernous hemangioma are summarized in **Tables 2** and **3**, respectively. While reviewing these nine cases, we observed various fallopian tube hemangioma findings, positions, and sizes. In some cases, a hemangioma of the fallopian tube was protruding into the tubal lumen or had a polypoid appearance. Similar to hemangiomas that may occur in other organs, it developed as an encapsulated, spongy mass and even appeared as mixed solid and cystic nodules. It was also observed as luminal dilatation filled with blood clots, slight bulges, or hemorrhagic masses or blood clots from the fimbriated end, even when the masses were not distinct. The anatomical locations of tumors also varied. There were two cases of unknown locations, three in the fimbrial region, and four in the ampulla and mid-portion. Tumor size was 0.3-3.5 cm (mean, 1.8 cm; median, 1.5 cm). Lesions < 1.0 cm in diameter were all incidentally detected, whereas those > 3.0 cm caused hemoperitoneum or a presentation of the cystic lesions that grew into the pelvic cavity. In three of the nine cases of fallopian tube hemangiomas, hemoperitoneum was found during surgery with a blood volume of 100 mL (two cases) and 500 mL (one case), respectively. Rupture of an undetected fallopian tube hemangioma can lead to hemoperitoneum with fatal consequences, and misinterpretation of this benign entity in a young woman may lead to radical surgery with subsequent loss of fertility.

Hemangioma of the fallopian tube can cause both rupture-induced hemoperitoneum and torsion, trauma, or inflammation by its mass effects.

In summary, the case described here, as in previous cases, confirms that fallopian tube hemangiomas are rare benign lesions. It is necessary to consider hemangioma in the differential diagnosis of fallopian tube masses. Proper diagnosis can be established only after histopathological examination. Such lesions are usually asymptomatic, but torsion, trauma, and extensive bleeding with subsequent hemoperitoneum can occur. Detailed investigations are necessary to clarify the pathogenesis of tumor development and growth of hemangioma in the fallopian tube.

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Disclosure of conflict of interest

None.

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