Pathol. Oncol. Res. (2017) 23:717–722
DOI 10.1007/s12253-016-0186-y

ORIGINAL ARTICLE

Anastomosing Hemangioma of the Ovary: A Clinicopathological Study of Six Cases with Stromal Luteinization

Pavel Dundr[1] · **Kristýna Němejcová**[1] · **Jan Laco**[2] · **Helena Skálová**[1] · **Lenka Bauerová**[1] · **Radoslav Matěj**[1,3] · **Daniela Fischerová**[4]

Received: 20 April 2016 / Accepted: 29 December 2016 / Published online: 3 January 2017

Abstract We report six cases of anastomosing hemangioma of the ovary. All lesions were unilateral and arose in 43 to 81 year old females. In all but one patient, the tumor was asymptomatic and represented incidental finding. The exception was a tumor associated with massive ascites and elevated CA 125. The tumors were, on cut section, spongy and dark violet in color. The size of tumors ranged from 0.5 to 3.5 cm. All lesions showed the same histological features and consisted of capillary sized anastomosing vessels with sinusoid-like pattern intermingled with sporadic medium sized vessels. Interestingly, in all cases there were areas of luteinized cells at the tumor periphery, which ranged from rare small nests to multiple and commonly confluent areas. In one tumor, components of mature adipose tissue were present. Immunohistochemically, all tumors were CD31 and CD34 positive. Other markers examined were negative, including; estrogen receptor, progesterone receptor, androgen receptor, and D2–40. Proliferative activity (Ki-67 index) was very low in all cases. Anastomosing hemangioma is a rare entity, only 8 lesions occurring in ovary has been described from its initial description in 2009. We report six additional cases with their clinicopathological correlation.

Keywords Anastomosing hemagioma · Capillary hemangioma · Ovary · Stromal luteinization · Urogenital tract

Part of this work was presented on 27th European Congress of Pathology, Belgrad, Serbia, 5–9 September 2015.

✉ Pavel Dundr
pdundr@seznam.cz

[1] Department of Pathology, First Faculty of Medicine Charles University and General University Hospital in Prague, Studnickova 2, 12800 Prague 2, Czech Republic

[2] The Fingerland Department of Pathology, Charles University, Faculty of Medicine and University Hospital Hradec Kralove, Hradec Kralove, Czech Republic

[3] Department of Pathology and Molecular Medicine, Thomayer Hospital, Prague, Czech Republic

[4] Gynecologic Oncology Center, Department of Obstetrics and Gynecology, First Faculty of Medicine Charles University and General University Hospital in Prague, Prague, Czech Republic

Introduction

Anastomosing hemangioma is a rare recently described entity initially reported in the urogenital tract on a series of 6 cases occurring in kidney and testis [1]. Since that, about 50 cases have been described in kidney, and sporadic cases have been reported in other organs of genitourinary tract including testis, spermatic cord, uterus, and urinary bladder [2–4]. However, this entity is not specific for urogenital tract and has been reported in other locations including liver, gastrointestinal tract (colon, small bowel), mesentery, adrenal gland, retroperitoneum, and soft tissues [5–7]. Regarding the ovary, only 8 cases of anastomosing hemangioma have been described in this location to date [2, 7, 8]. We report a series of 6 additional cases of anastomosing hemangioma of the ovary emphasizing their clinicopathological and morphological features, including a common finding of stromal luteinization.

Material and Methods

The archive files of participating departments were searched for vascular lesions of the ovary. Cavernous lesions and non-neoplastic vascular proliferation were excluded. Finally, we identified six cases of capillary-type hemangioma which were

included in the study. Histologic review of the hematoxylin and eosin-stained slides was performed in all cases and formalin-fixed paraffin-embedded (FFPE) tissue blocks were selected for immunohistochemical analysis. Immunohistochemical analysis was performed using the avidin-biotin complex method with antibody against the CD31 (clone JC70A, dilution 1:25, Dako, Glostrup, Denmark), CD34 (clone QBEND 10, dilution 1:50, Dako), D2–40 (clone D2–40, dilution 1:100, Dako), CD68 (clone PGM1, dilution 1:25, Dako), α-inhibin (clone R1, ready-to-use, Dako), calretinin (clone DAKCalret1, dilution 1:50, Dako), estrogen receptor (ER, clone 6F11, 1:200, Novocastra, Newcastle, UK), progesterone receptor (PR, clone 16, dilution 1:100, Novocastra), androgen receptor (AR, clone AR 441, dilution 1:100, NeoMarkers, Fremont, CA), and Ki-67 (clone Mib-1, 1: 50, Dako). Antigen retrieval was performed by including pretreatment in 0.01 M citrate buffer (pH 6.0) for 40 min in a water bath at 98 °C for CD31, CD34, D2–40, progesterone receptor and androgen receptor. Antigen heat-induced epitope retrieval was performed in 0.01 M citrate buffer (pH 9.0) for CD68, α-inhibin, calretinin, Ki-67, and estrogen receptor.

Results

The clinicopathological features are summarized in Table 1.

Clinical Findings

The tumors occurred in female patients aged 43 to 81 years (mean 66 years (SD = 11.4), median 68.5 years). Three cases involved the right ovary, 2 cases the left ovary, and in one case the laterality was unknown. The size ranged from 0.5 cm to 3.5 cm in the largest diameter. In all but one case, the tumors represented incidental findings and were clinically asymptomatic. The only symptomatic case was a tumor 3.5 cm in largest diameter associated with massive ascites (2.5 l) and elevated serum CA 125 (470 U/mL; normal value is 0–35 U/mL) (Figs. 1, 2, 3, 4 and 5).

Pathological Findings

Grossly, the tumors were in all cases relatively well demarcated spongy lesions confined to ovary. On cut section the tumors were dark violet in color with one exception (case No. 3) with a component of yellowish tissue 0.8 × 0.5 cm. Microscopically, all tumors showed typical features of anastomosing hemangioma and consisted of anastomosing proliferation of capillary-sized vessels intermingled with rare medium-sized vessels. The sinusoid-like architecture closely resembled splenic red pulp. The tumor cells showed mild nuclear variability without apparent atypia. Mitoses were absent. In all cases, scattered hobnail cells were present. Common findings were fibrin thrombi and hemorrhage. Numerous mononuclear cells were present inside the vascular spaces. In all cases areas of stromal luteinization consisting of large cells with eosinophilic or clear finely vacuolated cytoplasm can be found. In one case (case No. 5), rare Reinke crystalloids were present. The luteinized areas ranged from small and rare groups of cells (case No. 2), multiple larger groups (case No. 6) to large confluent group of cells (cases No. 1, 3, 4, 5). In all cases, these areas were located at the periphery of the vascular tumors with only rare luteinized cells intermingled with the tumor vessels. Moreover, in one tumor there was an area (0.8 × 0.5 cm) consisting of mature adipose tissue component intermingled with nests of luteinized cells.

Immunohistochemical Analysis

Immunohistochemically, the tumor cells showed in all cases expression of CD31 and CD34. Other markers examined were negative, including; estrogen receptor,

Table 1 Clinicopathological features of anastomosing hemangioma

Case No.	Age	Site	Size (cm)	Clinical manifestation	Follow-up	Stromal luteinization
1	66	ovary	0.5	incidental finding (HEBA because of metrorrhagia)	25 months, NED	confluent, periphery
2	43	left ovary	1.3 × 0.3	incidental finding (HEUA because of leiomyomas and benign ovarian cyst)	4 months, NED	rare small group of cells
3	69	right ovary	1.5 × 0.8	incidental finding (HEBA because of leiomyomas)	52 months, NED	confluent, periphery
4	81	right ovary	3.5 × 3 × 2.5	incidental finding (HEBA because of metrorrhagia due to adenomyosis)	NA	confluent, periphery
5	68	left ovary	3.5 × 3 × 1.8	ovarian tumor, ascites, increased CA125 (470 U/ml)	NA	confluent, mostly periphery
6	69	right ovary	1.2 × 0.8	suspected ovarian tumor (patient under surveillance because of lymphoma)	13 months, NED	multiple small nodules, periphery

HEBA hysterectomy with bilateral salpingo-oophorectomy, *HEUA* hysterectomy with unilateral salpingo-oophorectomy, *NA* not available, *NED* no evidence of disease

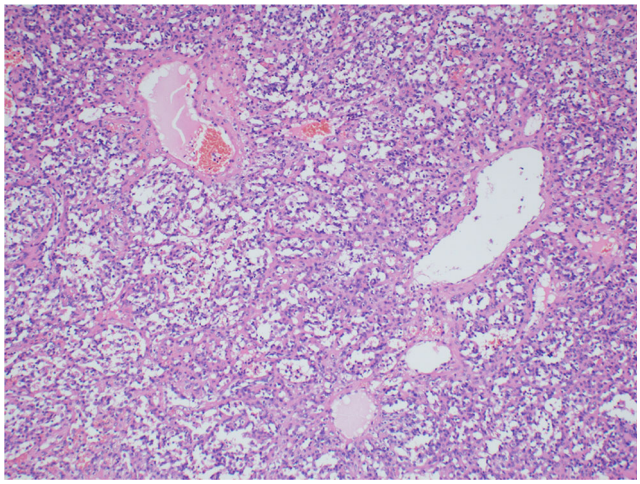

Fig. 1 Hemangioma of the ovary consisting of anastomosing small vessels and few larger medium-sized vessels (case no. 6, HE, 100 x)

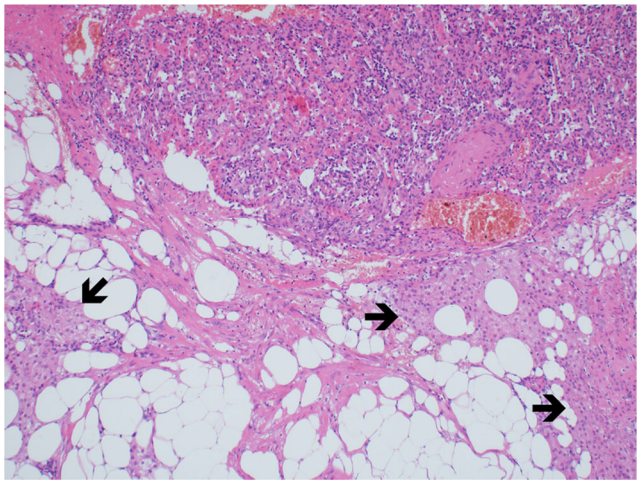

Fig. 3 Anastomosing hemangioma with component of adipose tissue. Note the luteinized cells intermingled with adipocytes (arrows) (case no. 3, HE, 100 x)

progesterone receptor, androgen receptor, and D2–40. The luteinized cells were positive with antibodies against α-inhibin and calretinin. CD68 was positive in mononuclear cells located in vascular spaces. Proliferative activity (Ki-67 index), even though estimated in areas of "hot spots", was in all cases very low (case No. 4 < 1%; case No. 1, 3 and 5 < 2%; case No. 2 and 6 < 4%).

Discussion

Hemangiomas of the ovary are rare lesions, less than 90 cases have been reported in the literature to date [2, 7–37]. The lesions are usually small and asymptomatic, but ovarian hemangiomas can be associated with pseudo-Meigs syndrome and a yet unnamed syndrome consisting of unilateral or bilateral hemangioma, elevation of CA 125, and massive ascites [13, 14, 20, 22, 36]. Histologically, more than half of reported cases were cavernous type and remaining cases were capillary type or mixed. Hemangiomas or florid vascular proliferation resembling hemangiomas can rarely arise in teratoma [38–41]. Based on the reported features of capillary hemangiomas described prior to the definition of anastomosing hemangioma in 2009, or after that but classified only as a capillary hemangioma, we believe that most of these cases should be classified as anastomosing hemangioma [9, 14, 18, 20, 25, 33]. To this regard, anastomosing hemangioma seems to be the most common type of capillary hemangioma occurring in ovary. Anastomosing hemangioma was initially described in the urogenital tract, however other reports described its occurrence in other organs and tissues and this entity is not specific for genitourinary organs [5–7]. The morphology of anastomosing hemangioma is

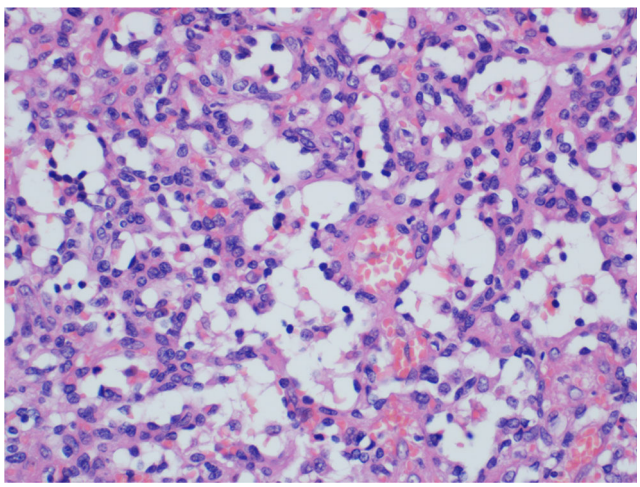

Fig. 2 Anastomosing hemangioma with mild nuclear variability and scattered hobnail cells (case no. 6, HE, 400 x)

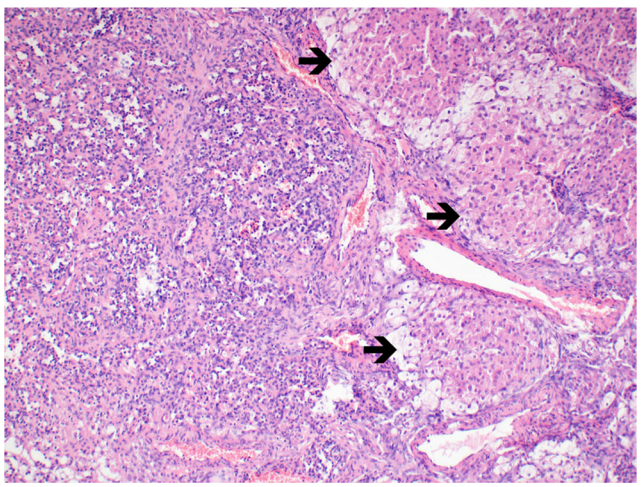

Fig. 4 Anastomosing hemangioma (left) with luteinized cells at the periphery (arrows) (case no. 5, HE, 100 x)

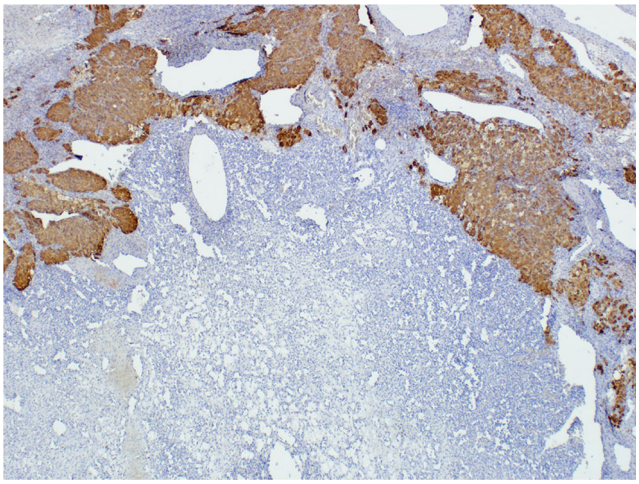

Fig. 5 Anastomosing hemangioma at the periphery with sheets of luteinized cells (case no. 5, α-inhibin, 40 x)

quite characteristic and encompasses non-lobular proliferation of capillary sized vessels with sinusoid-like arrangements resembling red pulp of the spleen, which are intermingled with moderate-sized "feeding" and "draining" vessels. Hobnail cells are common, as well as thrombi, extramedullary hematopoiesis and areas of hemorrhage. There is some variability in nuclei but nuclear atypias are generally absent. Mitoses are absent or rare.

The differential diagnosis of anastomosing hemangioma encompasses especially low grade angiosarcoma. In contrast to anastomosing hemangioma, angiosarcoma is characterized by presence of nuclear atypia, increased mitotic and proliferative activity, and common multilayering of tumor cells or presence of solid areas. Moreover, necrosis is commonly present. Necrosis can be present in the anastomosing hemangioma as well, usually in the center of the lesion together with other regressive changes. Nevertheless, the misdiagnosis of anastomosing hemangioma with well differentiated angiosarcoma could be a common event, at least according to the literature data [1, 4]. Other lesions, which can be confused with ovarian hemangioma, include epithelioid and infantile hemangioendothelioma, and non-tumorous vascular proliferation of ovarian hilus [42, 43]. Hemangioendothelioma is characterized by a focal component with solid or cord-like architecture. Moreover, cells with eosinophilic vacuolated cytoplasm representing the earliest stage of lumen formation are present. Cases of anastomosing hemangioma located in adipose tissue, either primarily or for example in kidney hilus, usually show infiltrative growth at the periphery and tumor vessels are intermingled with mature adipocytes. However, the lipomatous component can be on rare occasions a part of the tumor arising in area where adipose tissue does not normally occur [34]. This component was found in one of our cases, representing a substantial part of the tumor. In these cases, the differential diagnosis also includes myelolipoma. Moreover, in cases with prominent stromal luteinization, the differential diagnosis includes also steroidogenic tumors. Stromal luteinization is not a rare finding in ovarian hemangiomas [8, 10, 25, 32, 36]. There are two theories explaining such changes [10, 32]. The most probable hypothesis is that the non-functioning vascular tumors behave similarly like enlarged follicles causing pressure on the adjacent tissue leading to the development of theca-like luteinized stromal cells. The other hypothesis is that preexisting hyperestrogenic state from stromal luteinization stimulates development of ovarian hemangioma due to the growth stimulatory effects of estrogens on vessels. However, the absence of estrogen and progesterone receptors in endothelial cells in all our cases as well as in other studies concerning their expression, suggests that ovarian hemangiomas may occur independently of hormonal stimulation [16, 25, 35]. In addition, we assessed expression of androgen receptors, which were also negative. In our cases, luteinized cells were present in all cases. In one case, the luteinized cells were rare and formed a small group. However, in other 5 cases these areas were much more prominent. Interestingly, in one case we have found rare Reinke crystalloids, so these cells can be classified as Leydig cells.

In conclusion, anastomosing hemangioma of the ovary is rare vascular lesion, which can be misdiagnosed as an ovarian angiosarcoma. Awareness of this entity is essential for achieving a correct diagnosis. Moreover, the possibility of stromal luteinization should be considered, to avoid misdiagnosis with steroid cell tumor with pronounced stromal vascularization or mixed vascular-steroidogenic tumor.

Acknowledgements This work was supported by Ministry of Health, Czech Republic (Project RVO 64165), by Charles University in Prague (Project PRVOUK-P27/LF1/1, PRVOUK P37/11, UNCE 204024, and SVV UK 260256/2016), BBMRI_CZ LM2015089 and BBMRI_CZ LM2010004, and by OPPK (Research Laboratory of Tumor Diseases, CZ.2.16/3.1.00/24509).

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Montgomery E, Epstein JI (2009) Anastomosing hemangioma of the genitourinary tract: a lesion mimicking angiosarcoma. Am J Surg Pathol 33(9):1364–1369. doi:10.1097/PAS.0b013e3181ad30a7
2. Kryvenko ON, Gupta NS, Meier FA, Lee MW, Epstein JI (2011) Anastomosing hemangioma of the genitourinary system: eight cases in the kidney and ovary with immunohistochemical and ultrastructural analysis. Am J Clin Pathol 136(3):450–457. doi:10.1309/AJCPJPW34QCQYTMT

3. Omiyale AO (2015) Anastomosing hemangioma of the kidney: a literature review of a rare morphological variant of hemangioma. Ann Transl Med 3(11):151. doi:10.3978/j.issn.2305-5839.2015.06.16
4. Tao LL, Dai Y, Yin W, Chen J (2014) A case report of a renal anastomosing hemangioma and a literature review: an unusual variant histologically mimicking angiosarcoma. Diagn Pathol 9:159. doi:10.1186/s13000-014-0159-y
5. John I, Folpe AL (2016) Anastomosing hemangiomas arising in unusual locations: a Clinicopathologic study of 17 soft tissue cases showing a predilection for the Paraspinal region. Am J Surg Pathol. doi:10.1097/PAS.0000000000000627
6. Lin J, Bigge J, Ulbright TM, Montgomery E (2013) Anastomosing hemangioma of the liver and gastrointestinal tract: an unusual variant histologically mimicking angiosarcoma. Am J Surg Pathol 37(11):1761–1765. doi:10.1097/PAS.0b013e3182967e6c
7. O'Neill AC, Craig JW, Silverman SG, Alencar RO (2016) Anastomosing hemangiomas: locations of occurrence, imaging features, and diagnosis with percutaneous biopsy. Abdom Radiol (NY). doi:10.1007/s00261-016-0690-2
8. Metodiev D, Ivanova V, Omainikova B, Boshnakova T (2015) Ovarian anastomosing hemangioma with stromal luteinization: a case report. Akush Ginekol (Sofiia) 54(9):58–61
9. Akbulut M, Bir F, Colakoglu N, Soysal ME, Duzcan SE (2008) Ovarian hemangioma occurring synchronously with serous papillary carcinoma of the ovary and benign endometrial polyp. Ann Saudi Med 28(2):128–131
10. Anand MS, Shetty S, Mysorekar VV, Kumar RV (2012) Ovarian hemangioma with stromal luteinization and HCG-producing mononucleate and multinucleate cells of uncertain histogenesis: a rare coexistence with therapeutic dilemma. Indian J Pathol Microbiol 55(4):509–512. doi:10.4103/0377-4929.107793
11. Comunoglu C, Atasoy L, Baykal C (2010) Ovarian hemangioma occurring synchronously with contralateral mature cystic teratoma in an 81-year-old patient. Ups J Med Sci 115(4):297–299. doi:10.3109/03009734.2010.502602
12. Correa-Rivas MS, Colon-Gonzalez G, Lugo-Vicente H (2003) Cavernous hemangioma presenting as a right adnexal mass in a child. P R Health Sci J 22(3):311–313
13. Erdemoglu E, Kamaci M, Ozen S, Sahin HG, Kolusari A (2006) Ovarian hemangioma with elevated CA125 and ascites mimicking ovarian cancer. Eur J Gynaecol Oncol 27(2):195–196
14. Gehrig PA, Fowler WC Jr, Lininger RA (2000) Ovarian capillary hemangioma presenting as an adnexal mass with massive ascites and elevated CA-125. Gynecol Oncol 76(1):130–132. doi:10.1006/gyno.1999.5648
15. Grant JW, Millward-Sadler GH (1986) Haemangioma of the ovary with associated endometrial hyperplasia. Case report Br J Obstet Gynaecol 93(11):1166–1168
16. Gucer F, Ozyilmaz F, Balkanli-Kaplan P, Mulayim N, Aydin O (2004) Ovarian hemangioma presenting with hyperandrogenism and endometrial cancer: a case report. Gynecol Oncol 94(3):821–824. doi:10.1016/j.ygyno.2004.06.021
17. Gunes HA, Egilmez R, Dulger M (1990) Ovarian haemangioma. Br J Clin Pract 44(12):734–735
18. Gupta R, Singh S, Nigam S, Khurana N (2006) Benign vascular tumors of female genital tract. Int J Gynecol Cancer 16(3):1195–1200. doi:10.1111/j.1525-1438.2006.00523.x
19. Jurkovic I, Dudrikova K, Boor A (1999) Ovarian hemangioma. Cesk Patol 35(4):133–135
20. Kaneta Y, Nishino R, Asaoka K, Toyoshima K, Ito K, Kitai H (2003) Ovarian hemangioma presenting as pseudo-Meigs' syndrome with elevated CA125. J Obstet Gynaecol Res 29(3):132–135
21. Kim SS, Han SE, Lee NK, Choi KU, Joo JK, Suh DS, Kim HY, Kim KH (2015) Ovarian cavernous hemangioma presenting as a large growing mass in a postmenopausal woman: a case report and review of the literature. J Menopausal Med 21(3):155–159. doi:10.6118/jmm.2015.21.3.155
22. Koh LW, Sun YL, Koh PH, Chiu HY, Chen SY, Huang MH (2007) Ovarian capillary hemangioma presenting as pseudo-Meigs' syndrome: a case report. J Minim Invasive Gynecol 14(3):367–369. doi:10.1016/j.jmig.2006.10.030
23. Loverro G, Cormio G, Perlino E, Vicino M, Cazzolla A, Selvaggi L (1998) Transforming growth factor-beta1 in hemangioma of the ovary. Gynecol Obstet Investig 46(3):210–213
24. McBurney RP, Trumbull M (1955) Hemangioma of the ovary with ascites. Miss Doct 32(10):271–274
25. Miliaras D, Papaemmanouil S, Blatzas G (2001) Ovarian capillary hemangioma and stromal luteinization: a case study with hormonal receptor evaluation. Eur J Gynaecol Oncol 22(5):369–371
26. Mirilas P, Georgiou G, Zevgolis G (1999) Ovarian cavernous hemangioma in an 8-year-old girl. Eur J Pediatr Surg 9(2):116–118. doi:10.1055/s-2008-1072225
27. Mitra B, Sengupta S, Rai A, Mehta J, Quader AR, Roy S, Borges A (2013) Ovarian haemangioma: A rare case report. Int J Surg Case Rep 4(11):981–984. doi:10.1016/j.ijscr.2013.07.029
28. M'Pemba Loufoua-Lemay AB, Peko JF, Mbongo JA, Mokoko JC, Nzingoula S (2003) Ovarian torsion revealing an ovarian cavernous hemangioma in a child. Arch Pediatr 10(11):986–988
29. Ozana M, Formanek P, Sula F, Silhan J (1994) Ovarian hemangioma with torsion. Ceska Gynekol 59(1):18–20
30. Pethe VV, Chitale SV, Godbole RN, Bidaye SV (1991) Hemangioma of the ovary–a case report and review of literature. Indian J Pathol Microbiol 34(4):290–292
31. Rivasi F, Philippe E, Walter P, de Marco L, Ludwig L (1996) Ovarian angioma. Report of 3 asymptomatic cases. Ann Pathol 16(6):439–441
32. Savargaonkar PR, Wells S, Graham I, Buckley CH (1994) Ovarian haemangiomas and stromal luteinization. Histopathology 25(2):185–188
33. Schoolmeester JK, Greipp PT, Keeney GL, Soslow RA (2015) Ovarian hemangiomas do not harbor EWSR1 rearrangements: Clinicopathologic characterization of 10 cases. Int J Gynecol Pathol 34(5):437–444. doi:10.1097/PGP.0000000000000171
34. Tran TA, Pernicone P (2012) Anastomosing hemangioma with fatty changes of the genitourinary tract: a lesion mimicking angiomyolipoma. Cent European J Urol 65(1):40–42. doi:10.5173/ceju.2012.01.art13
35. Uppal S, Heller DS, Majmudar B (2004) Ovarian hemangioma–report of three cases and review of the literature. Arch Gynecol Obstet 270(1):1–5. doi:10.1007/s00404-003-0584-8
36. Yamawaki T, Hirai Y, Takeshima N, Hasumi K (1996) Ovarian hemangioma associated with concomitant stromal luteinization and ascites. Gynecol Oncol 61(3):438–441. doi:10.1006/gyno.1996.0170
37. Ziari K, Alizadeh K (2016) Ovarian hemangioma: a rare case report and review of the literature. Iran J Pathol 11(1):61–65
38. Akbulut M, Zekioglu O, Terek MC, Ozdemir N (2009) Florid vascular proliferation in mature cystic teratoma of the ovary: case report and review of the literature. Tumori 95(1):104–107
39. Baker PM, Rosai J, Young RH (2002) Ovarian teratomas with florid benign vascular proliferation: a distinctive finding associated with the neural component of teratomas that may be confused with a vascular neoplasm. Int J Gynecol Pathol 21(1):16–21
40. Itoh H, Wada T, Michikata K, Sato Y, Seguchi T, Akiyama Y, Kataoka H (2004) Ovarian teratoma showing a predominant hemangiomatous element with stromal luteinization: report of a case and review of the literature. Pathol Int 54(4):279–283. doi:10.1111/j.1440-1827.2004.01621.x
41. Pongsuvareeyakul T, Settakorn J, Khorana J, Khunamornpong S (2015) Ovarian teratoma with predominant hemangiomatous

component in early childhood. J Pediatr Adolesc Gynecol 28(1): e1–e3. doi:10.1016/j.jpag.2014.02.013

42. Illueca C, Machado I, Garcia A, Covisa A, Morales J, Cruz J, Traves V, Almenar S (2011) Uncommon vascular tumor of the ovary. Primary ovarian epithelioid hemangioendothelioma or vascular sarcomatous transformation in ovarian germ cell tumor? Arch Gynecol Obstet 284(6):1589–1591. doi:10.1007/s00404-011-2036-1
43. Prus D, Rosenberg AE, Blumenfeld A, Udassin R, Ne'eman Z, Young RH, Ariel I (1997) Infantile hemangioendothelioma of the ovary: a monodermal teratoma or a neoplasm of ovarian somatic cells? Am J Surg Pathol 21(10):1231–1235