ANNALI ITALIANI DI CHIRURGIA

Digital Edition
e-publish on-line
ISSN 2239-253X
Direttore Nicola Picardi

A case of three rare uterine neoplasms in the same surgical specimen

Ann Ital Chir, Digital Edition 2020, 9
pii: S2239253X20031527 - Epub, Jan. 20
free reading: www.annitalchir.com

Antonio Giuliani*, Lucia Romano*, Federica Romanzi**, Giacomo Giubbolini***, Gino Coletti***, Nicoletta Di Stefano**, Jean Nicolas Le'Clerc****, Mario Schietroma*, Francesco Carlei*, Leonardo Di Stefano**

**Department of General Surgery. Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy*
***Department of Obstetrics and Gynecology, University of L'Aquila, L'Aquila, Italy*
****UOC Anatomia Patologica, ASL1 Abruzzo, Ospedale San Salvatore, L'aquila, Italy*
*****Hospital Clínico Quirúrgico "Joaquín Albarrán", Facultad de Medicina "Victoria de Girón", Universidad de Ciencias Médicas de la Habana, Cuba*

A case of three rare uterine neoplasms in the same surgical specimen

BACKGROUND: *Uterine sarcomas are mesenchymal tumors; they are rare, representing less than 2-3% of all uterine malignancies. Among them, we can define four types: leiomyosarcoma (LMS), endometrial stromal sarcoma (ESS), Adenosarcoma and Carcinosarcoma. This last type was recently reclassified by FIGO as a Mullerian type of the endometrial adenocarcinoma. Therefore, today only the first three types are histologically considered.*
METHODS: *In this paper, we reported a case of simultaneous presence of three different rare neoplasms in the same surgical specimen, resulting from a hysterectomy of a premenopausal woman. The woman presented to the ED with a six-months history of vaginal bleeding. Given the complexity of the clinical picture, we suggested hospitalization in our Department of Gynecology, to perform appropriate diagnostic tests. Because of the persistent hemorrhage and the absence of required fertility preservation, a laparotomic hysterectomy with bilateral annessiectomy was performed.*
RESULTS: *The postoperative histology of the specimen described the myoma at the fundus as a leiomyosarcoma. The myoma of the uterine anterior wall appeared as an endometrial stromal sarcoma of low-grade. Moreover, an intramural cavernous hemangioma of 3 cm in diameter was reported at the uterine corpus.*
CONCLUSION: *All these described pathologies have no specific clinic characteristics; the most common symptom is abnormal uterine bleeding. To date, hysterectomy and bilateral salpingo-oophorectomy are the standards of care in the management of all early stage uterine sarcomas.*
To our knowledge, cases of LMS, ESS and cavernous haemangioma coexisting in the same patient have not been reported in literature to date. The pathogenesis of this combination remains to be elucidated.

KEY WORDS: Cavernous hemangioma, Endometrial stromal sarcoma, Leiomyosarcoma, Uterine sarcomas

Introduction

Uterine sarcomas are mesenchymal tumors; they are rare, representing less than 2-3% of all uterine malignancies, with annual incidence estimated at 3 cases per 100000 women, and with an average age of onset around 56-58 years[1,2]. Among them, we can define four types: leiomyosarcoma (LMS), endometrial stromal sarcoma (ESS), Adenosarcoma and Carcinosarcoma [3]. This last type was recently reclassified by FIGO as a Mullerian type of the endometrial adenocarcinoma. Therefore, today only the first three types are histologically considered.
Consisting of up to 60% of uterine sarcomas, LMS is the most common type. It represents less than 2% of all uterine malignancies [1] and, according to the population-based Surveillance, Epidemiology and End Results

Pervenuto in Redazione: Ottobre 2019. Accettato per la pubblicazione Novembre 2019
Correspondence to: Lucia Romano, MD. Department of General Surgery, Department Of Biotechnological and Applied Clinical Sciences, University of L'Aquila, 67100 Coppito (AQ), Italy (e-mail: lucia.romano@graduate.univaq.it)

(SEER) database from the National Cancer Institute [4], its annual incidence is less than two women per 100000. ESS is the second most common category of mesenchymal uterine tumors (about 10% of them) [5,6], counting for approximately 0.2% of all uterine malignancies, with an annual incidence of 1 to 2 per million women and with a minor biological aggressivity than LMS [7,8]. Adenosarcoma accounts for 5% of uterine sarcomas, and it is common in the post-menopausal age. Today, the diagnosis of uterine sarcoma is histologically performed after surgery, because the preoperative symptoms are non-specific and similar to those associated with uterine benign fibroids.

Uterine cavernous hemangioma is a benign vascular tumor. In this anatomical site, it is very infrequent, and only about 50 cases of this disease were found in the literature over the last century [9].

In this paper, we reported a case of simultaneous presence of three different rare neoplasms in the same surgical specimen, resulting from a hysterectomy of a premenopausal woman: leiomyosarcoma, endometrial stromal sarcoma and uterine cavernous hemangioma.

Case Report

A 48-years old premenopausal woman presented to the ED with a six-months history of vaginal bleeding. She referred that the hemorrhage was resistant to pharmacological control with tranexamic acid, recommended by her general practitioner. The patient had no relevant family history and denied chronic diseases except for morbid obesity (BMI=38). She referred heavy menstrual periods with a regular rhythm of 28/30 days and lasting 7 days. Her obstetric history consisted of two miscarriage in early age (8-9 weeks) and four cesarean sections (longitudinal laparotomies). She also referred a large consumption of cigarettes (about 20 cigarettes per day) from the third pregnancy. In 2013 she was diagnosed with multiple submucosal myomas and between 2013 and 2016 underwent three hysteroscopic resections for this reason, never reporting any anatomopathological evidence of malignancy.

Given the complexity of the clinical picture, the persistence of symptoms and resistance to medical treatment, we suggested hospitalization in our Department of Gynecology, to perform appropriate diagnostic tests. Bimanual examination showed widespread abdominal pain and enlarged uterine corpus volume with fundus at umbilicus, not mobile, but pelvic examination was limited by abdominal wall thickness. Transvaginal ultrasound showed a uterus increased in volume with multiple myomas, the bigger localized in the fundus and measuring 11x9x10 cm with well-defined borders and heterogeneous pattern, with IOTA color score 1-2. The cleavage planes with the rectum and the bladder fundus were clear. The study of the uterine cavity showed due polyploid neoplasms, well limited, originated by the inner layer of the myometrium, measuring respectively 3 and 4 cm. There was no clinical or sonographic evidence of ascites. A magnetic resonance imaging (MRI) of the abdomen and pelvis was performed. The MRI confirmed the large fundal fibroid with areas of degeneration (positive enhancement after contrast administration) and evidenced a further nodule on the anterior wall of the uterus with intramural and submucosal growth, measuring 4x3 cm and characterized by an inhomogeneous internal signal. The ovaries appeared normal and there was no associated lymphadenopathy. Subsequent investigation also included tumor marker estimation, that showed normal values of Ca125, Ca15.3, Ca 19.9 and He-4. The hemoglobin value was 7 g/dL (hypochromic microcytic anemia), and this required the transfusion of two units of red blood cells and a single-unit plasma transfusion.

Because of the persistent hemorrhage and the absence of required fertility preservation, a laparotomic hysterectomy with bilateral annessiectomy was performed. No visible findings suggestive of malignancy on the operative field were reported.

The postoperative histology of the specimen described the myoma at the fundus as a leiomyosarcoma with diffuse significant cytological atypia and necrosis areas in absence of mitotic activity (<5 HPF) with an Actin + immunophenotype and multiple p16 an p53 positive areas (Figs. 1A, B, C). The myoma of the uterine ante-

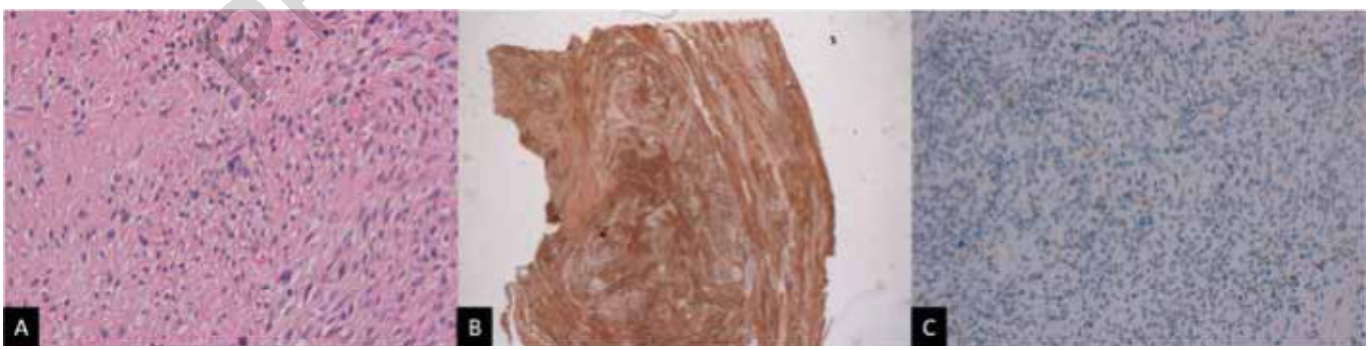

Fig. 1: LMS. A: Atipie, 40X. B: Actina. C: p53.

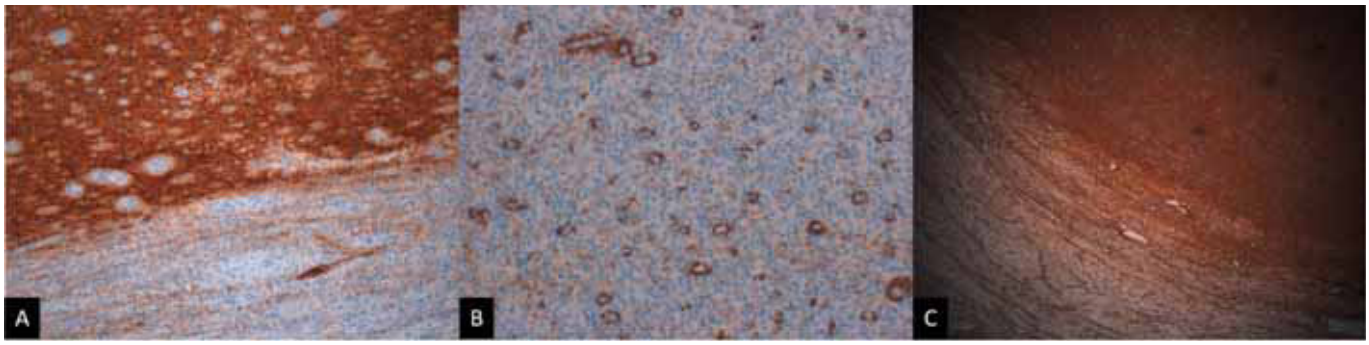

Fig. 2: ESS. A: CD 10, passaggio miometrio-ESS. B: Actina nello stroma. C: Vimentina 10X, passaggio miometrio-ESS.

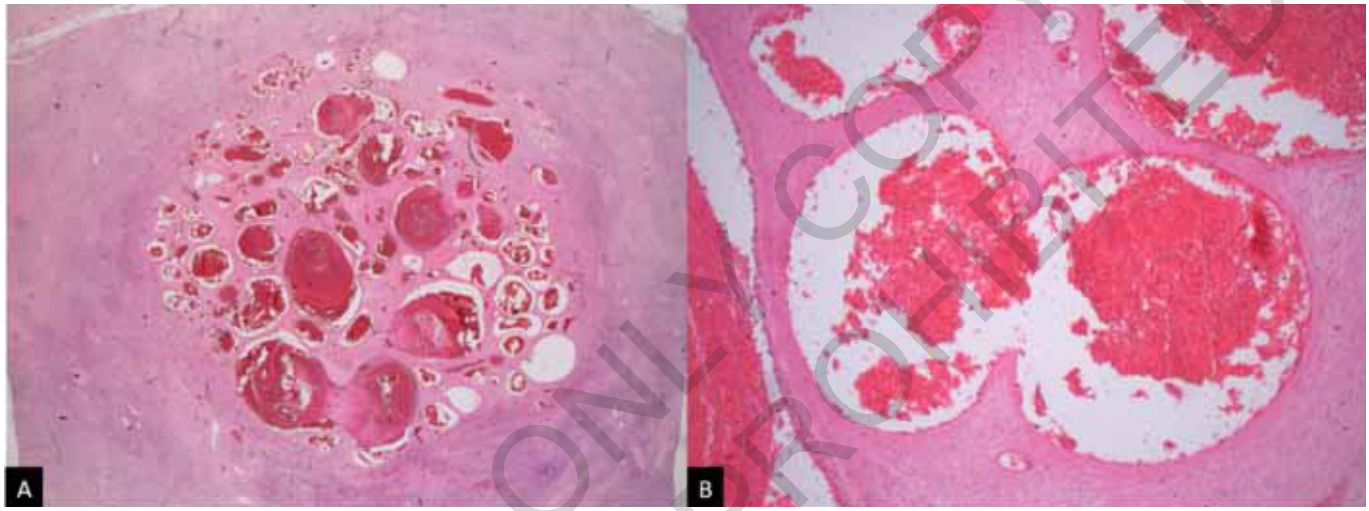

Fig. 3: Intramural cavernous hemangioma.

rior wall appeared as an endometrial stromal sarcoma of low-grade infiltrating myometrium for half of its thickness with immunophenotype CD10+, Actin+, Vimentin+, Cyclin D1-, and low grade of proliferation (Figs. 2A, B, C). Moreover, an intramural cavernous hemangioma of 3 cm in diameter was reported at the uterine corpus (Figs. 3 A, B). Tubes and ovaries were devoid of significant alterations.

The patient, after an oncological consultation, was dismissed on post-operative day 9 because of the occurrence of an incisional hernia that required surgical correction with prothesis. One-year oncological follow-up did not show any metastasis or disease recurrence.

Discussion

Uterine sarcomas are comprised of: malignant mixed Mullerian tumor (MMMT), which is also called carcinosarcoma, because it has both mesenchymal and epithelial components [10]; leiomyosarcoma (LMS), which arises from myometrial smooth muscle; endometrial stromal sarcoma (ESS), which originates from the endometrial stroma. There are several risk factors associated with uterine sarcomas, such as pelvic radiation, tamoxifen, and some genetic conditions, in particular hereditary leiomyomatosis and renal cell cancers and hereditary retinoblastoma [11,12].

LMS is the most common type of uterine sarcoma (about 60%). It is extremely aggressive, and it is associated with a poor prognosis. Moreover, it shows resistance to standard therapies, with consequently high rates of recurrence and progression [13,14]). Some studies have demonstrated 5-year survival to be between 25 and 76%, but a survival in case of metastatic disease at the time of diagnosis of 10–15% [15]. Recurrence rates vary from 45 to 75% [14,16]. The incidence of LMS appears to be connected with age (with a spike in incidence during the perimenopausal years), African–American race, and prolonged use of tamoxifen [17,18]. Also radiation exposure and some inherited genetic conditions (i.e. hereditary retinoblastoma and Li-Fraumeni syndrome) seem to be related to an increased risk[14]. Chromosomal aberrations have been reported across the LMS genome, with frequent deletions affecting chromosomal arms 2p, 2q, 10q and 13q, as well as amplifications on 1p, 5q and 8q [19,20]. Histologically, LMS is

characterized by moderate to severe cytological atypia, high mitotic index, coagulative cell necrosis. Some characteristics are in common with uterine smooth muscle tumours of uncertain malignant potential (STUMPs), and immunohistochemistry can help to differentiate these entities. In particular, LMS typically shows a positive stain for smooth muscle actin, desmin and caldesmon [17].

After LMS, ESS is the second most common type of mesenchymal uterine tumors (less than 10%). It is composed of cells that morphologically resemble proliferative-phase endometrial stroma. ESSs can be classified into low-grade (LGESS) and high-grade (HGESS) [21,22]. LGESS is common in middle-aged females with mean age of 39 years, while the HGESS is seen in older age group with a mean age of 61 years at presentation and is usually aggressive, with local recurrences and distant metastasis that can occur even 20 years after initial diagnosis [3,23,24]. The underlying aetiology of these tumors is poorly understood, although they seem to be linked with estrogenic levels, treatment with tamoxifen, obesity and diabetes [25]. Specific translocation t(7;17) (p15;q21) and chromosome deletion on 7p may play a role in the development of ESS [23]. The second most frequent abnormality is t(6;7)(p21;p15) [22]. Immunohistochemically, the tumor cells are usually positive for CD10, vimentin, actins, WT-1, IFITM1, ER, and PR. In some areas, also keratin may be positive [22].

Hemangiomas are benign tumors originated from endothelial cells of blood vessels or pericytes of the basal lamina of the endothelium. Histologically, they are characterized by irregular anastomosing vascular spaces, with intraluminal blood or thrombus. They appear in two forms: capillary and cavernous. Both types can be found in the uterus, more commonly in the upper cervix and corpus, but with diffuse pattern of distribution [26]. The cavernous uterine hemangioma was first described in 1897 as an incidental discovery from an autopsy of a young woman who, after delivering twins, developed anemia and dyspnea that led her to dead [27]. The incidence still remains unclear, and the current literature identifies fewer than 50 cases [26]. It may be congenital or acquired. The congenital type could be associated with hereditary diseases such as Klippel-Trenaunay syndrome, hereditary haemorrhagic telangiectasia, tuberous sclerosis, Maffucci syndrome, and Kasabach-Merritt syndrome [9]. In case of acquired forms, hemangiomas develop in association with surgery, trophoblastic disease, pelvic inflammatory disease, cancer of the endometrium and many theories propose that hormones play a crucial role in their development [28]. In fact, estrogens can cause an increase in endothelial progenitor cells and angiogenic factors such as matrix metalloproteinase, vascular endothelial growth factor, nitric oxide, and other related factors [9]. At the immunohistochemical examination, the cells lining the vascular spaces are immunoreactive for endothelial markers [26,29].

All these described pathologies have no specific clinic characteristics. The most common symptoms in case of leiomyosarcoma are abnormal uterine bleeding (56%), palpable pelvic mass or enlarged uterus (54%), abdominal bloating and pelvic pressure or pain (22%) [14,17,30]. Also in case of ESS, presenting symptoms are nonspecific and may comprise pelvic pain, abdominal distension and abnormal vaginal bleeding that occurs in about 90% of women [21]. ESS could also be asymptomatic in 25% individuals [23]. Concerning hemangiomas, a majority of them is incidentally discovered, but they could be associated with abnormal vaginal bleeding [9].

In our case, the woman complained about abnormal uterine bleeding, that, as we can see, is a nonspecific symptom and it is common to all of these pathological situations.

To date, hysterectomy and bilateral salpingo-oophorectomy are the standards of care in the management of all early stage uterine sarcomas. This can therefore be considered effective in cases of LMS confined to the uterine corpus or limited to the pelvis and also in cases of LGESS, as regional lymph nodes are usually not involved in early-stage disease [13,21]. Adjuvant chemotherapy or radiotherapy have not been shown to have beneficial impact on survival outcomes in all uterine sarcoma subtypes [17,21]. Also in case of hemangiomas refractory to conservative treatments, although the best treatment option remains unclear, hysterectomy may be considered [26].

In our patient, the ESS was post-surgically classified as a stage IB of the FIGO system (limited to uterus, with less than half myometrial invasion) [31]. According to the literature, this stage is associated with a 5-year survival of over 60%, with a very low rate of recurrence [26].

The LMS was also staged as IB (limited to uterus, measuring more than 5 cm); the absence of involvement of other pelvic tissues, the presence of a whole pseudo-capsule and the low mitotic activity can be all considered positive prognostic factors.

Conclusion

The patient in the present case was a 48-year-old premenopausal woman. The chief complaint of this patient was abnormal uterine bleeding, resistant to pharmacological therapies, and she was treated with hysterectomy with bilateral annessiectomy. We want to share our experience about this because, although sarcoma is a rare disease (1/20000 hysterectomies for uterine lesions), the gynaecologist should keep it in mind in the differential diagnosis when an expansive lesion of the uterus is detected.

To our knowledge, cases of LMS, ESS and cavernous haemangioma coexisting in the same patient have not been reported in literature to date. The pathogenesis of this combination remains to be elucidated. No inherit-

ed common conditions seem to be detectable. It could be supposed that the development involves common risk factors, or it could be just a coincidental event. Future studies could be useful to investigate synchronous tumors.

Riassunto

I sarcomi uterini sono rari tumori mesenchimali e rappresentano meno del 2-3% di tutte le neoplasie uterine. Tra questi, possiamo definire quattro tipi: leiomiosarcoma (LMS), sarcoma stromale endometriale (ESS), adenosarcoma e carcinosarcoma. Quest'ultimo tipo è stato recentemente riclassificato dalla FIGO come sottotipo mulleriano di adenocarcinoma endometriale. Pertanto, oggi solo i primi tre tipi sono considerati da un punto di vista istologico. Nel nostro caso, riportiamo un caso di presenza simultanea di tre diverse neoplasie rare nello stesso campione chirurgico, risultante da un'isterectomia di una paziente in età pre-menopausale. La donna giungeva presso il nostro centro con un'anamnesi positiva per sanguinamento vaginale da sei mesi. Data la complessità del quadro clinico, abbiamo suggerito il ricovero nel nostro Dipartimento di Ginecologia, per eseguire test diagnostici appropriati. A causa della persistente emorragia e dell'assenza di necessità di conservare la fertilità, è stata eseguita un'isterectomia laparotomica con annessiectomia bilaterale. Esame anatomopatologico del pezzo chirurgico ha descritto il mioma del fondo uterino come leiomiosarcoma. Il mioma della parete anteriore è risultato essere un sarcoma stromale endometriale di basso grado. È stato inoltre riportato un emangioma cavernoso intramurale di 3 cm di diametro a livello del corpus uterino. Tali patologie descritte non hanno caratteristiche cliniche specifiche; il sintomo più comune è il sanguinamento uterino anomalo. Ad oggi, l'isterectomia con annessiectomia bilaterale rappresenta lo standard di cura per tutti i sarcomi uterini in fase iniziale. Per quanto noto, ad oggi non sono stati riportati in letteratura casi di LMS, ESS ed emangioma cavernoso coesistenti nella stessa paziente. La patogenesi di questa combinazione resta da chiarire.

References

1. D'Angelo E, Prat J: *Uterine sarcomas: A review.* J Gynecol Oncol. 2010;116(1):131-39.

2. Harlow BL, Weiss NS, Lofton S: *The epidemiology of sarcomas of the uterus.* J Natl Cancer Ins, 1986; 76(3):399-402.

3. Adiga CP, Gyanchandani M, Goolahally LN, Itagi RM, Kalenahalli KV: *Endometrial stromal sarcoma: An aggressive uterine malignancy.* J Radiol Case Rep, 2016;10(9).

4. Brooks SE, Zhan M, Cote T BC: S*urveillance, epidemiology, and end results analysis of 2677 cases of uterine sarcoma 1989–1999.* Gynecol Oncol, 2004; 93:204-08.

5. Wen KC, Horng HC, Wang PH, et al.: *Uterine sarcoma Part I-Uterine leiomyosarcoma: The Topic Advisory Group systematic review.* J Obs Gynecol, 2016; (55):463-71.

6. Livi L, Paiar F, Shah N, et al.: *Uterine sarcoma: twenty-seven years of experience.* Int J Radiat Oncol Biol Phys, 2003; 57(5):1366-373.

7. Hendrickson MR, Tavassoli FA, Kempson RL, et al.: *Mesenchymal tumors and related lesions*. World Heal Organ Classif Tumors Pathol Genet Tumors Breast Female Genit Organs IARC Press Lyon, 2003; 124(7):233-44.

8. Xiu XX, Wang HL, Yun-Yi L, Fan-Dou K, Jin-Ping H: *Endometrial stromal sarcoma in combination with mixed type endometrial carcinomas: A case report and literature review*. Med (United States). 2017; 96(49):2-7.

9. Aka KE, Horo GA, Fomba M, Kouyate S, Koffi AK, Konan S, et al.: *A rare case of important and recurrent abnormal uterine bleeding in a post partum woman caused by cavernous hemangioma: A case report and review of literature*. Pan Afr Med J, 2017; 28:1-85.

10. Wang WL, Soslow R, Hensley M, Asad H, Zannoni GF de N, M, :et al. *Histopathologic prognostic factors in stage I leiomyosarcoma of the uterus: a detailed analysis of 27 cases.* Am J Surg Pathol, 2011; 35:522-29.

11. Ganjoo KN: *Uterine sarcomas.* Curr Probl Cancer, 2019; 43(4):283-88.

12. Alberta Health Services: *Uterine sarcoma.* Clinical practice Guideline Gyne-007. Version 2. September 2013.

13. Roberts ME, Aynardi JT, Chu CS: *Uterine leiomyosarcoma: A review of the literature and update on management options.* Gynecol Oncol, 2018; 151(3):562-72.

14. *Linee guida AIOM (Associazione Italiana di Oncologia Medica). Sarcomi dei tessuti molli e GIST*. 2018; Cap. 10, 60-80.

15. Seagle BL, Sobecki-Rausch J, Strohl AE , et al.: *Prognosis and treatment of uterine leiomyosarcoma: A National Cancer Database study.* Gynecol Oncol, 2017; 145(1):61-70.

16. Giuntoli RL, Metzinger DS, Di Marco CS, et al.: *Retrospective review of 208 patients with leiomyosarcoma of the uterus: prognostic indicators, surgical management, and adjuvant therapy*. Gynecol Oncol, 2003; 89(3):460969.

17. Cui RR, Wright JD, Hou JY: *Uterine leiomyosarcoma: a review of recent advances in molecular biology, clinical management and outcome.* BJOG An Int J Obstet Gynaecol, 2017; 124(7):1028-37.

18. Gockley AA, Rauh-Hain JA del CM: *Uterine leiomyosarcoma: a review article.* Int J Gynecol Cancer, 2014; 24:1538-542.

19. Cuppens T, Moisse M, Depreeuw J, et al.: *Integrated genome analysis of uterine leiomyosarcoma to identify novel driver genes and targetable pathways.* Int J Cancer, 2018; 142(6):1230-243.

20. Raish M, Khurshid M, Ansari MA, et al.: *Analysis of molecular cytogenetic alterations in uterine leiomyosarcoma by array-based comparative genomic hybridization.* J Cancer Res Clin Oncol, 2012; 138:1173-186.

21. Benson C, Miah AB: *Uterine sarcoma - Current perspectives.* Int J Womens Health, 2017; 9:597-606.

22. Nucci MR: *Practical issues related to uterine pathology: Endometrial stromal tumors.* Mod Pathol, 2016; 29 (Suppl 1):S92-103.

23. Puliyath G NM: *Endometrial stromal sarcoma: A review of the literature.* Indian J Med Paediatr Onco, 2012; 33(1):1-6.

24. Tavassoli FA, Devilee P: *Pathology and Genetics: Tumours of the Breast and Female Genital Organs.* WHO Classification of Tumours series - Volume IV. Lyon, France: IARC Press. 2004. Article number: 133.

25. Felix AS, Cook LS, Gaudet MM, Rohan TE, Schouten LJ, Setiawan VW WL, et al.: *The etiology of uterine sarcomas: A pooled analysis of the epidemiology of endometrial cancer consortium*. Br J Cancer, 2013; 108(3):727-34.

26. Chou WY, Chang HW: *Uterine hemangioma: A rare pathologic entity.* Arch Pathol Lab Med, 2012; 136(5):567-71.

27. Johnson C, Reid-Nicholson M, Deligdisch L, Grinblat S NS: *Capillary hemangioma of the endometrium: A case report and review of the literature.* Arch Pathol Lab Med, 2005; 129(10):132-329.

28. Malhotra S, Sehgal A NR: *Cavernous hemangioma of the uterus.* Int J Gynaecol Obstet, 1995; 51:159-160. Int J Gynaecol Obs. 199AD; 51:159-60.

29. Giuliani A, Romano L, Coletti G, et al.: *Lymphangiomatosis of the ileum with perforation: A case report and review of the literature.* Ann Med Surg (Lond), 2019; 41:6-10.

29. Exacoustos CL, Romanini ME, Amadio A, et al.: *Can gray-scale and color Doppler sonography differentiate between uterine leiomyosarcoma and leiomyoma?* J Clin Ultrasound, 2007; 35(8):449-57.

30. Prat J: *FIGO staging for uterine sarcomas.* Int J Gynaecol Obstet, 2009; 104(3):177-78.