EJGO European Journal of Gynaecological Oncology

Rapid enlargement of endometrial stromal sarcoma after uterine fibroid embolization for presumed adenomyosis: a case report and literature review

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Summary

Uterine sarcomas have rarely been diagnosed after uterine artery embolization. It remains unclear whether the diagnostic work-up is required prior to such embolization to prevent a missed diagnosis of sarcomas and a delay in providing definitive treatment. Because of the rarity and heterogeneity of endometrial stromal neoplasms, little is known about their epidemiology, pathogenesis, and molecular pathology. The authors report a case of low-grade endometrial stromal sarcoma (ESS) diagnosed after uterine fibroid embolization. Although they performed laparoscopic biopsy of the rapidly growing uterine mass, they could not detect the ESS. Although rare, ESS should be considered in the differential diagnosis of uterine fibroid enlargement. It is essential to assess the risk of malignancy by taking into account the patient's clinical symptoms, results of the physical exam, and imaging findings prior to uterine artery embolization. Pathologic diagnosis should include an adequate biopsy sample and the use of molecular genetic testing.

Key words: Endometrial stromal sarcoma; Uterine leiomyoma; Embolization.

Introduction

Endometrial stromal sarcoma (ESS) is a rare neoplasm that accounts for approximately 0.2% to 1.0% of all uterine malignancies. However, it is also implicated in an estimated 10% to 15% of malignancies having a mesenchymal component, and the prognostic significance of these tumors is unclear [1].

ESS presents as a rapidly growing pelvic mass that may be accompanied by vaginal bleeding and abdominal or pelvic pain. Imaging, particularly magnetic resonance imaging (MRI), has an increasing role in the assessment of these malignancies; it is useful in the evaluation of pelvic masses at presentation, for adequate staging, and consequently to determine the appropriate management approach [2].

Although the pathogenesis of ESS is poorly understood, specific cytogenetic aberrations and molecular changes have recently been elucidated. In particular, almost all ESSs are characterized by the overexpression of estrogen receptors (ER) and of progesterone receptors (PR), which have been reported in approximately 70% and 95% of cases, respectively [3]. Specifically, the presence of the JAZF1–SUZ12 (formerly the JAZF1–JJAZ1) fusion identifies a large proportion of endometrial stromal nodules (ESNs) and low-grade ESSs [4].

In almost all instances, uterine fibroid embolization (UFE) is performed in the absence of histologic confirmation and thus carries the risk that an underlying sarcoma will be overlooked. The present patient was diagnosed as having adenomyosis with symptoms, and the authors decided to perform UFE to preserve the uterus. Suspecting that the uterine mass might be malignant, they performed pelvic computed tomography (CT) and laparoscopic biopsy of the mass after embolization. However, they were unable to make the diagnosis of a rapidly growing ESS. Hence, in young, premenopausal women, an adequate tissue sample, review by an experienced pathologist, and a prompt decision by the surgeon are very important in the diagnosis and treatment of ESS. Furthermore, molecular testing and immunohistochemical staining are also helpful in confirming the diagnosis.

Case Report

A 36-year-old nulliparous woman was referred to the Hematooncology Department with the following clinical presentation: hypermenorrhea, abdominal and pelvic pain, and anemia (Hb 7.0 g/dl) that had become progressively worse over the past three years. Her menstrual cycle was regular and lasted seven days, accompanied by severe dysmenorrhea. The patient had a history of ectopic pregnancy and had undergone bilateral salpingectomy ten years earlier. Abdominal and gynecological examinations revealed a large, irregularly shaped uterus. On transvaginal sonography (TVS) the findings of an enlarged uterus (11.96×7.04 cm) and a thickened anterior uterine wall (4.28 cm) with a normal vascularization pattern suggestive of adenomyosis were confirmed.

Revised manuscript accepted for publication October 8, 2015

Eur. J. Gynaecol. Oncol. - ISSN: 0392-2936
XXXVII, n. 6, 2016
doi: 10.12892/ejgo3349.2016

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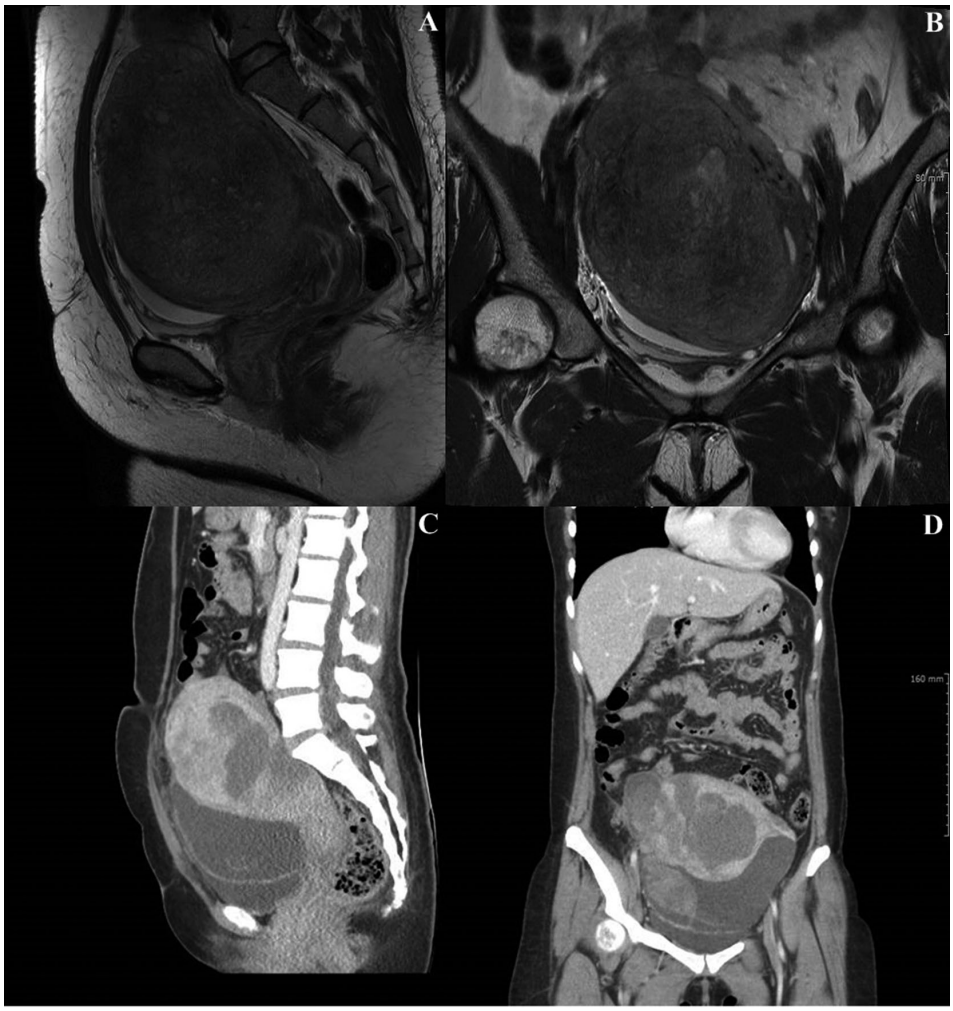

Figure 1. — Preoperative MRI (A, B) was performed prior to uterine artery embolization. MRI confirmed marked anterior myometrial thickening and zonal layer disruption on the right side of the uterus. In sagittal (A) and coronal (B) views, this lesion showed strong and homogeneous enhancement on the gadolinium-enhanced T1-weighted image. The presumptive diagnosis was adenomyosis. Five months later, pelvic CT showed an enlarged uterine mass and increased fluid collection around the uterus (C, sagittal view; D, coronal view).

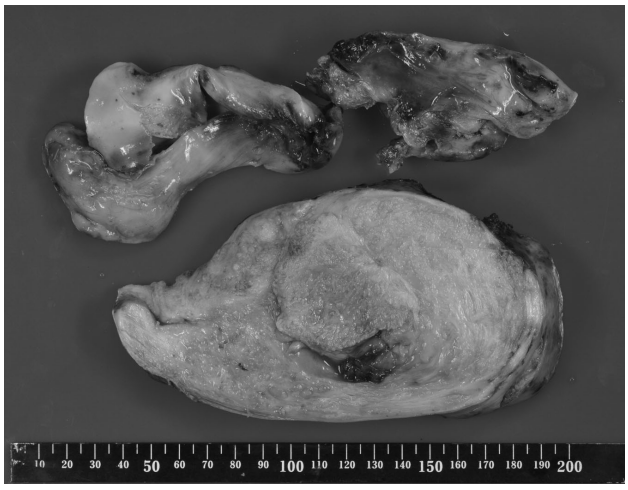

Figure 2. — Gross specimen consisting of the complete uterus, which measured 16.0×12.0×8.0 cm and weighed 744.0 g. On sectioning, a solid mass is found (6.5×4.5 cm), with some yellowish necrosis in the uterine cavity, and it appears that the mass had invaded the myometrium.

The patient was treated with iron therapy and oral contraceptives and was scheduled for regular follow-up visits. One year later she was admitted to the emergency room because of abdominal pain. Pelvic CT showed that the uterus was about ten cm wide, with heterogeneous enhancement of adenomyosis. After one year, she presented again, this time with menorrhagia, metrorrhagia, and abdominal pain. UFE was performed since the patient wished to preserve the uterus. Preoperative MRI confirmed marked myometrial thickening of the right uterine wall, which was especially prominent anteriorly; in addition, the zonal layer was disrupted in T2–weighted image (WI), with strong, homogeneous enhancement of the uterine corpus on the right side visible on the gadolinium-enhanced T1-WI. Based on these findings, the authors diagnosed adenomyosis (Figures 1A and B). The patient was discharged from the hospital after UFE with no further problems.

Three months later, the menorrhagia had improved. However, on TVS, an irregularly shaped hypoechoic lesion, 5×6 cm, was noted on the right side of the uterus. The dysmenorrhea had become worse, and pelvic CT was performed. The size of the uterine mass was found to have decreased slightly (from 14×11 to 12×9 cm), with internal cystic or necrotic change. Multiloculated soft tissue was observed on the uterine body on the right side along the lateral border and appeared to be slightly larger than on previous

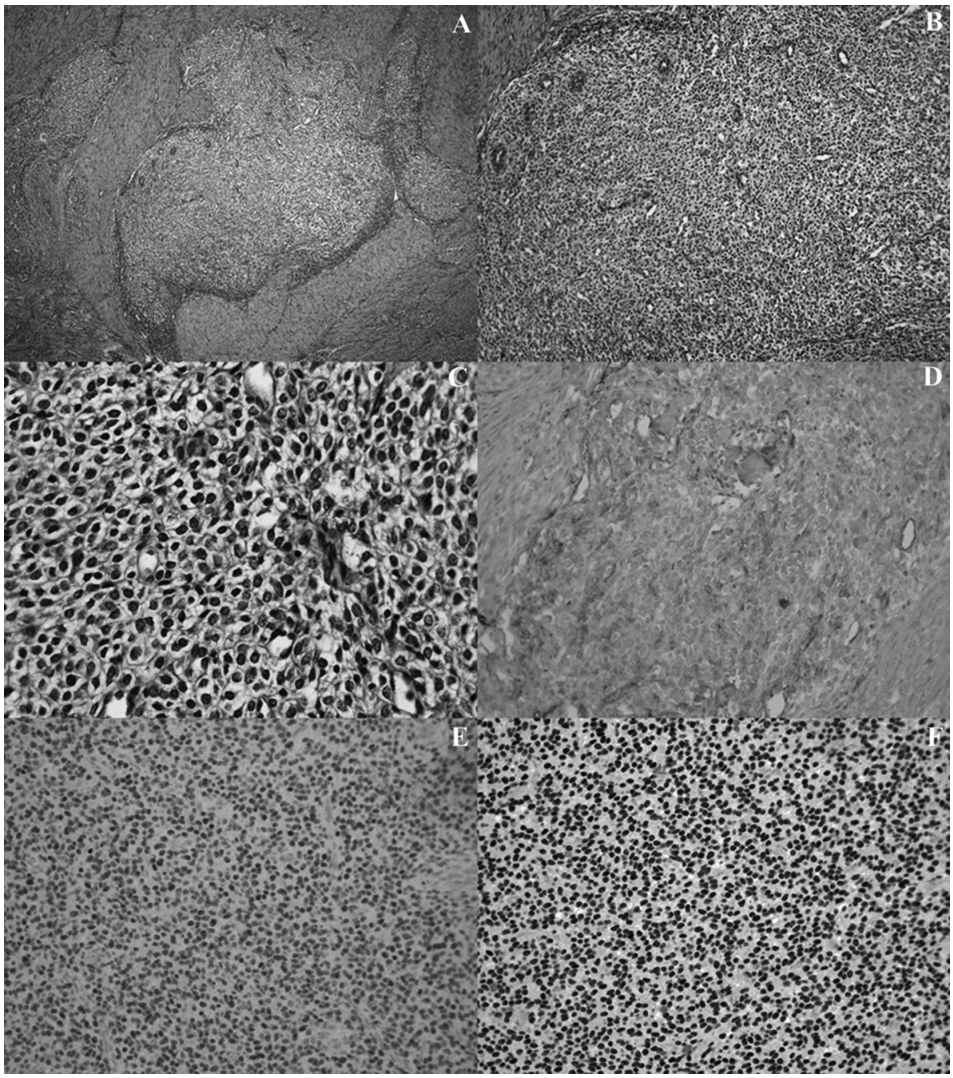

Figure 3. — Immunohistological findings include minimal nuclear pleomorphism, a low mitotic index, and an infiltrative growth pattern within the myometrium. (A) H&E stain (magnification ×40); (B) H&E (×100); (C) H&E (×400). Immunohistochemical investigation showing CD10-positive cells. (D) CD10 (×200). (E, F) There is strong nuclear antibody staining for estrogen (E, ×200) and progesterone (F, ×200) receptors.

imaging. The authors suspected a mild reduction in volume of the uterine adenomyotic lesion, with cystic or necrotic change and extrauterine intravascular adenomyomatosis, and they also considered the less likely possibility of ESS with vascular involvement. After the patient was advised to undergo a total hysterectomy, but she and her husband declined in hopes of preserving the uterus for baby. Therefore, the authors decided to obtain a laparoscopic biopsy specimen of the uterine mass, and found severe pelvic adhesions with a tubular uterine mass on the right side. They then obtained a 0.7 cm × 0.6 cm biopsy specimen of the uterine mass, which showed irregular tongues of proliferative endometrial stromal cells partly containing endometrial glands. Thus, a differential diagnosis between florid adenomyosis and low-grade ESS was required. The Ki-67(proliferation index) was 7%, and a working diagnosis of adenomyosis was made. However, a definitive diagnosis was difficult because these findings could not be detected in the biopsy specimen.

One month later, the patient was admitted to the hospital with abdominal pain and rapidly increasing abdominal distention. Pelvic CT indicated a malignant mass in the uterus with a peritoneal inclusion cyst (Figures 1C and D), and obstruction of the right ureter with mild hydronephrosis was suspected. The patient underwent total abdominal hysterectomy with bilateral oophorectomy, as well as pelvic lymphadenectomy, omentectomy, and adhesiolysis. Chest CT showed probable multiple metastatic nodules in the left upper lobe and the right lower lobe of the lungs, and a single-port, video-assisted thoracoscopic right lower lobe wedge resection was performed. ESS had formed a large extrauterine pelvic mass and a right horn mass and had multifocally metastasized to the right infundibulopelvic ligament, the right round ligament, the right parametrial lymph nodes, and the lung.

On gross examination, the uterus was found to be diffusely enlarged and measured 16.0×12.0×8.0 cm and weighed 744.0 grams. On sectioning of the specimen, there was a polypoid, pale-yellow solid mass growing into the endometrial cavity, and the entire myometrium had a trabeculated appearance caused by diffuse permeation of cords and nodules of tumor into the myometrium with a yellow and reddish-brown, soft, fish-flesh like cut surface (Figure 2). Microscopic examination revealed that the tumor was a low-grade ESS with adenomyosis and endometriosis intermingled at the tumor periphery. Irregular nests of tumor cells of variable sizes had invaded the surrounding myometrium, and evenly distributed small blood vessels were noted (Figures 3A and B). The tumor was composed of cells that resemble the stromal cells found in proliferative

endometrium, having uniformly round or oval nuclei, a finely granular chromatin pattern, small or no nucleoli, and rare mitosis (Figure 3C). On immunohistochemistry, the tumor cells were positive for CD10 (Figure 3D), ER (Figure 3E), and PR (Figure 3F).

The patient was diagnosed with a low-grade ESS (IVb) and was discharged two weeks after surgery with no complications and was prescribed on aromatase inhibitor (letrozole, 2.5 mg/day) for six months. At the three-month follow-up visit, the authors obtained chest CT and positron-emission tomographic CT images and results of all these studies were normal, and at the one-year follow-up, the patient was in good clinical condition.

Discussion

ESS is a rare, hormone-sensitive uterine malignancy that typically affects women of either reproductive or postmenopausal age (the greatest incidence among those between 40 and 55 years of age, with an annual incidence of one to two per million women). The typical clinical manifestation of the disease is vaginal bleeding, with associated pelvic/abdominal pain in some cases [3].

Routine gynecological imaging is unable to discriminate between leiomyoma and ESS, so a preoperative diagnosis can be challenging. TVS in combination with color imaging or power Doppler that demonstrates increased vascularity, irregularity, and random distribution of blood vessels can help differentiate benign from malignant tumors. For the assessment of uterine lesions, Kurjak *et al.* reported a sensitivity of 90.9% and a specificity of 99.8% with TVS using color Doppler [5], however, these findings are highly controversial.

MRI may prove to be a powerful tool in the management of these tumors, allowing characterization of the initial stage and also differentiating them from the more common endometrial carcinomas [6]. Irregular contours of the tumor and signs of degeneration should alert the physician to the possibility of malignancy in MRI with T2-weighted sequences [7, 8]. These tumors have a tendency to invade the lymphatic and vascular systems and show wormlike extension bands of low signal intensity within areas of myometrial involvement ("bag of worms") on T2-WI, corresponding to preserved bundles of myometrium [7]. Compared with endometrial carcinoma, ESS is usually larger in size, with more contrast enhancement, irregular margins, nodular extension into the myometrium, and marginal nodularity due to extension of the tumor along vessels and lymphatics [6]. Rarely, ESS can appear as a myometrial mass mimicking intramural leiomyoma with cystic degeneration. In these cases, intramyometrial ESS can be differentiated based on its rapid and invasive growth, lower degree of enhancement, lymphatic and vascular invasion, higher incidence of necrosis, peripheral hypointense rim on T2-weighted images, and enhanced marginal irregularity [6, 9].

In the uterine corpus, ESS characteristically shows prominent, fingerlike myometrial infiltration with lymphovascular permeation. ESS in its so-called classic form is composed of a proliferation of small, round, monomorphic cells with scanty cytoplasm and round-to-oval nuclei with smooth nuclear contours, reminiscent of the non-neoplastic proliferative phase of endometrial stroma [9]. It also contains a rich, arborizing network of small arterioles around which the tumor cells are concentrically arranged. Mitotic activity can be variable but is generally not prominent (usually less than five mitotic figures per ten high-power fields). Necrosis can also be present, although it is typically not extensive and is ischemic in nature [6].

In the first operation, the authors found irregular tongues of proliferative endometrial stromal cells partly containing endometrial gland with a low Ki-67 (proliferation index) 7% and, accordingly, diagnosed florid adenomyosis. One month later, in the second operation, they found mild cytologic atypia and 0 to 1 mitotic figures per 10 HPF, and the cells were CD10-positive, ER-positive, PR-positive, and partly positive for desmin and they diagnosed ESS. Considering the difference in features between adenomyosis and ESS, an adequate tissue sample, examination by an experienced pathologist, and molecular testing were very important to the definitive diagnosis of ESS. This applies only to hysterectomy specimens that allow adequate tumor sampling (at least one section per centimeter of the tumor-involved area); when a more limited tissue sample is obtained, immunohistochemical characterization and molecular studies are important.

Low-grade ESSs frequently contain chromosomal rearrangements that result in JAZF1–SUZ12 fusion or equivalent genetic fusions. With the increasing use of cytogenetics in the early 1990s, it was discovered that the majority of ESSs harbor chromosomal translocations that are recurrent (non-random), with the most commonly reported translocation being t(7;17)(p16;q21), followed by t(6;7) or other forms of 6p rearrangement, t(10;17)(q22;p13), and t(X;17)(p21-p11;q23) [6, 10]. The fusion oncoproteins JAZF1-SUZ12 and JAZF1-PHF1 are believed to cause transcriptional dysregulation, and oncogenic influences are probably mediated through altered transcriptional control in endometrial stromal progenitor cells [10]. Immunohistochemically, nearly all reported JAZF1 low-grade ESSs, irrespective of the genotype, show positive staining for CD10, ER, and PR, with a generally diffuse staining pattern in adequately fixed tumor samples [6, 11]. There may be focal patchy staining of smooth muscle actin, caldesmon, and/or desmin, with more extensive staining of smooth muscle markers in JAZF1 low-grade ESSs showing smooth muscle differentiation. In keeping with its usual low mitotic activity, JAZF1 low-grade ESS typically shows a low Ki67 proliferation index (< 5%) [7, 11]. Nuclear cyclin D1 expression is typically weak and focal (< 25% of tumor cells and < 5% immunohistochemically) in JAZF1 low-grade ESS [12]. Although the present authors could not perform JAZF1 testing because the pathologic

Table 1. — *Case reports of endometrial stromal sarcomas(ESS) discovered following uterine artery embolization for presumed uterine fibroids.*

Author	Age (yrs)	Symptom	Investigations	Time since UAE (mo)	Treatment (Pathology)	ER	PR	CD10	Size	Adjuvant treatment	Prognosis
Goldberg *et al.*, 2004 [16]	45	Dysmenorrhea, menorrhagia	US	13	TAH+RSO followed by LSO+debulking (leiomyosarcoma+ low-grade ESS)				13.2× 9.3× 10.2 cm	CT, RT	Expire (31 (months)
Buzaglo *et al.*, 2008 [8]	45	Menorrhagia, bloating	US and MRI	6	TAH+BSO (high grade ESS)	Negative	Negative	Focal positive	8×9 cm	CT, RT	Expire (21 (months)
Soo Nyung Kim *et al.*, 2009 [17]	31	Lower abdominal pain	US and MRI	12	TAH+BSO+PLND (low grade ESS)				6.1× 4.4 cm	RT	
Present study	39	Dysmenorrhea, heavy menstrual bleeding	Investigations	5	TAH+BSO+PLND+ omentectomy (low grade ESS)	Positive	Positive	Positive	11×8 cm	Aromatase inhibitor	Survival

UAE: Uterine artery embolization; CT: Chemotherapy; RT: Radiotherapy; TAH: total abdominal hysterectomy; RSO: right salpingo oophorectomy; LSO: left salpingo oophorectomy; BSO: both salpingo oophorectomy; PLND: pelvic lymph node dissection.

specimen was in a poor state of preservation, the result of molecular tests on the first laparoscopic uterine mass biopsy might be helpful in the early diagnosis of ESS.

Standardized systemic therapy in ESS is not established, and the role of comprehensive surgical staging, including pelvic and para-aortic lymphadenectomy, remains controversial. Generally, ESS is associated with a good ten-year survival rate for both early and advanced stages of the disease (from 89% in Stage I to 66% in Stage IV). However, some have reported recurrences at three months to 23 years after treatment, with a median interval of approximately three years [3]. As a result of multivariate analysis, the most important prognostic factors reported are FIGO stage, tumor diameter, menopausal status, tumor grade, and tumor-free resection margins [3, 13]. A prompt diagnosis and timely intervention are keys to improving patient survival.

ER status should be determined in these cases, since it represents a potential therapeutic target. Although hormonal therapy has been shown to stabilize disease or induce a remission, this effect depends on the patient's receptor status. Aromatase inhibitors, including letrozole, appear to be promising agents that can be used as either adjuvant or first-line treatment [14]. Because this tumor is rare, one can hardly expect that novel molecularly targeted therapies will be specifically developed against ESS. Radiation therapy may also have a palliative role in managing pain, bleeding, and compression of surrounding organs [3].

Approximately 10% of ESS cases confined to the uterus at the time of diagnosis show pulmonary metastasis during the follow-up period [15]. In the case reported here, ESS could metastasize rapidly after uterine artery embolization (within five months).

Three additional cases of endometrial stromal sarcomas have been reported that were diagnosed after uterine artery embolization (Table 1). Goldberg *et al.* concluded that the lack of clinical response to a technically successful embolization should alert physicians to the need for further evaluation to detect possible sarcoma [16]. Buzaglo *et al.* concluded that an assessment of risk for malignancy based on clinical symptoms, results of a physical exam, and imaging findings is essential prior to uterine artery embolization [8]. Kim *et al.* suggested that any patient who does not respond to UFE in the management of a uterine fibroid should undergo biopsy or surgery for the definitive pathological exclusion of a malignancy [17]. Delay in the diagnosis of a sarcoma is the worst-case scenario of embolization, as in the case presented here. Common complaints such as excessive vaginal bleeding, pelvic pain, or pressure symptoms should alert the physician to consider sarcoma as a possible diagnosis. All reported cases of ESS post UFE were in premenopausal women (31 to 45 years of age). The symptoms were improved after embolization and pain, bleeding, menometrorrhagia, enlargement of uterine mass. The operation was performed and ESS was confirmed after five to 12 months. Immunohistochemical staining was not done in all cases. Postoperative chemotherapy and radiation therapy were carried out, and two patients died after 21 months [8, 17]. In three cases, chemotherapy and radiation therapy led to a poor prognosis in advanced ESS after embolization (Table 1). These sarcomas were probably misdiagnosed before the UFE procedures and after the procedure shrank in size for a short time owing to the reduced blood supply, but a few months after the procedure they started to grow again.

Conclusion

Although the risk of ESS is very low in young or premenopausal patients, any patient who undergoes a UFE procedure should be counseled regarding the risk of embolizing an undiagnosed uterine sarcoma. In addition, any patient who has not responded to UFE should undergo

biopsy or surgery to definitively rule out malignancy on pathological grounds. More genetic insights into uterine sarcomas can be expected with the application of next-generation sequencing technology.

Acknowledgement

This study was supported by a grant from the Department of Obstetrics and Gynecology, The Catholic University of Korea.

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