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Case Reports

Leiomyosarcoma: a rare malignant transformation of a uterine leiomyoma

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Summary

The malignant transformation of a uterine leiomyoma is still debated and, if it occurs, it is very rare. The case of a patient affected by one small leiomyoma is described. Diagnosis was made postoperatively on histopathological examination. The case reported here is meant to underline the need to keep all uterine myomas in check since the transition into leiomyosarcomas (LMSs) may occur with an evolution over a time period which has not been established so far. Specific receptors for luteinizing hormone / human chorionic gonadotropin (LH/hCG) have also been identified in the myometrium of several animal species, including humans. Conventional LMSs express estrogen receptors (ER), progesterone receptors (PR), and androgen receptors (AR) in 30-40% of cases. In comparison with other more common uterine malignancies, uterine LMSs bear some resemblance to type 2 endometrial carcinomas and high-grade serous carcinomas of ovary/fallopian tube origin, based on their genetic instability, frequent p53 abnormalities, aggressive behavior, and resistance to chemotherapy. It could be useful to understand with further researches if hormonal stimulation could be a contributing factor of uterine leiomyoma transformation into LMS. Until today the oncogenic mechanisms underlying the development of uterine LMSs remain elusive.

Key words: Leiomysarcoma; Uterus; Leiomyoma; Ovarian stimulation.

Introduction

Uterine sarcomas are rare tumors that account for approximately 1% of female genital tract malignancies and 3% to 7% of uterine cancers [1]. Although the aggressive behavior of most cases is well recognized, their rarity and histopathological diversity has contributed to the lack of consensus on risk factors for poor outcome and optimal treatment [2]. Histologically, uterine sarcomas were first classified into carcinosarcomas, accounting for 40% of cases, leiomyosarcomas (LMSs) (40%), endometrial stromal sarcomas (10% to 15%), and undifferentiated sarcomas (5% to 10%).

In most instances, uterine smooth muscle tumors (USMTs) are readily diagnosed as either benign or malignant. Rare patients whose smooth muscle tumors fail to meet LMS diagnostic criteria will experience recurrence, and occasional cases of LMS patients experience a protracted clinical disease course [3]. For these reasons a new classification is catching on: smooth muscle tumors of uncertain malignant potential (STUMP) are a heterogeneous group of neoplasms, from both the histological and clinical point of view. Due to the rarity of these tumors, the literature on the topic is limited; a consensus on their diagnosis, malignant potential, monitoring, and treatment has still not been reached [4-8]. The clinical behaviour of these neoplasms is also poorly understood. The majority of cases follow a benign clinical course, however a few can metastasize as either tumor of low malignant potential or LMSs [9]. Until today leiomyomas and LMSs are believed to develop independently and are not progressive. This belief is based on population studies, as well as genetic and cytogenetic profiles of these tumors and the fact that they lack shared mutations and transformations. LMSs are usually asymptomatic until they reach a size large enough to cause pain or bleeding. In cases in which the initial radiographic impression is not worrisome, rapid growth during the interval between imagings is an indication for resection. Most LMSs occur in perimenopausal and postmenopausal women; the average age of a woman with LMS is 50 years. However, premenopausal women may develop them. Most LMSs metastasize within two years of diagnosis. In this case report the authors would like to highlight that malignant transformation of uterine leiomyoma can occur over the years.

Case Report

A 43-year-old female patient presented at the gynaecology clinic complaining of a left anechoic adnexal cyst. She was a non-smoker and had a body mass index within the normal range. The patient attained menarche at the age of 14 years and had a regular cycle with four-day flow every 28 days. In the year 2000 a

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transvaginal pelvic ultrasound revealed a small (1.0 × 0.7 cm) solitary intramural leiomyoma of the posterior wall of the uterine body. In the year 2002 she had undergone one successful IVF cycle (a long stimulation protocol with Decapeptyl 3.75 mg + Menogon 75 UI + Profasi HP 5,000 UI) for primary infertility of male origin. She responded well to stimulation and produced eight eggs. Three embryos were transferred. This treatment was successful and a twin gestation was achieved (one boy and one girl). In the year 2006 she conceived spontaneously and she delivered a healthy girl at term. The patient was asymptomatic and physical examination was normal. She had no prior history of vaginal bleeding or abdominal pain. Preoperative assessment tests were all normal, including a full blood count, urea, glucose, clotting screen, hepatitis B-C status, and tumor markers. Transvaginal ultrasound examination confirmed a solitary left anechoic adnexal cyst (25 x 15 mm), an intramural leiomyoma (two cm in diameter, slightly larger than the previous ultrasound performed in the year 2000) of the posterior wall of the uterine body and no evidence of intra-abdominal fluid collection was detected. The magnetic resonance imaging confirmed these data. The patient underwent a left monolateral laparotomic salpingectomy without complications. Intraoperative findings showed a normal upper abdomen and no palpable lymph nodes. An extemporaneous histologic examination of the cyst was performed. While waiting for the outcome of histology, the surgical team decided to remove the uterine myoma. The pathological examination on frozen section revealed an hydrosalpinx with tubal endometriosis, but the final histopathological results of the uterine specimen showed an unexpected "cellular leiomyoma with a central area of malignant transformation into LMS (more than ten mitoses per ten high-power fields) desmin +, actin +, p16 +, Ki67 +, in 1% of the neoplastic cells". Two months later the patient underwent total abdominal hysterectomy; the histologic examination showed no presence of leiomyosarcomatous tissue. No further treatments were performed and until today the patient is asymptomatic and physical examination is normal.

Discussion

Analyzing the evolution of the case under examination, and in light of the several US scanning checks carried out over the years on the patient, it is likely that the very small-sized intramural myoma may have undergone malignant transformation. After excluding carcinosarcoma, LMS has become the most common subtype of uterine sarcoma. However, it accounts for only 1–2% of uterine malignancies. Most occur in women over 40 years of age who usually present with abnormal vaginal bleeding (56%), palpable pelvic mass (54%), and pelvic pain (22%). Signs and symptoms resemble those of the far more common leiomyoma and preoperative distinction between the two tumors may be difficult. Only very rarely does a LMS originate from a leiomyoma. The minimal pathological criteria for the diagnosis of LMS are more problematic and, in such cases, the differential diagnosis has to be made, not only with a variety of benign smooth muscle tumors that exhibit atypical histologic features and unusual growth patterns but also with STUMP. The diagnosis of these tumors is often challenging, as interpretative difficulties and subjectivity can be encountered when analysing any of the three histological features: cytologic atypia, mitotic index, and coagulative tumor cell necrosis. These three features are called the Stanford criteria and were developed by Bell *et al.* [5].

Cytologic atypia

The adjacent nonneoplastic myometrium may be used as an internal control for the patient's baseline smooth muscle histology. Cytologic atypia is assessed by determination of nuclear size, examination of membrane contours, and evaluation the prominence and number of nucleoli. The mitotic index aids in classifying the tumor.

Mitotic index

By itself, the mitotic index is not an independent predictor of malignancy. Mitotically active leiomyomas are well studied and reported. These are defined as smooth muscle tumors with up to 20 mitoses/ten high power fields (HPF), but they are devoid of atypia and tumor cell necrosis. Although this feature alone does not denote malignancy, when other worrisome features are present, mitotic activity becomes extremely important in assessing malignant potential. To measure the mitotic index, find the most mitotically active area of the tumor (but avoid areas adjacent to hyalinized necrosis) and count yen HPF (×40).

Coagulative tumor cell necrosis

Of the three features discussed, coagulative tumor cell necrosis seems to be the most predictive histologic feature of malignancy. Coagulative tumor cell necrosis is characterized by an abrupt change of viable myocytes adjacent to necrotic myocytes without an intervening sclerotic edge. Features predictive of malignancy include tumor cell necrosis (regardless of other features), infiltrative borders (recognized by the adjacent normal myometrium splayed and separated by the myxoid stroma), and mitoses greater than two per ten HPF. Some early reports of myxoid smooth muscle tumors found that tumors characterized by a mitotic index of zero per ten HPF, bland cytology, and infiltrative borders were associated with poor outcomes [10]. Although these findings have not been reproduced to date, they should probably be diagnosed with care; a STUMP category may be most appropriate. The term STUMP is sometimes applied to cases in which there are indeterminate features of malignancy or a combination of features that are unusual and therefore are not reported extensively in the literature. This term should be reserved for cases in which the malignant potential really is unknown, and it should be used sparingly. STUMP is essentially a non-diagnosis, and it is fraught with frustration for clinicians and patients. Most studies of STUMP report benign outcomes, which probably reflect the fact that the term is overutilized. If the tumor has features that are usually benign but if rare cases of recurrence are known, the term "low recurring potential" may be preferable to STUMP, because that term conveys more information about the predicted and known malignant potential [5, 11].

Immunohistochemistry and molecular biology

Several immunohistochemical and molecular genetic studies on uterine LMSs have been reported [4, 12–18]. LMSs usually express smooth muscle markers such as desmin, h-caldesmon, smooth muscle actin, and histone deacetylase 8 (HDCA8). Conventional LMSs express estrogen receptors (ER), progesterone receptors (PR), and androgen receptors (AR) in 30-40% of cases. Whereas a variable proportion of uterine LMSs has been reported as being immunoreactive for c-KIT, no c-KIT mutations have been identified [19]. Recent studies have shown statistically significant higher levels of Ki67 in uterine LMSs compared with benign smooth muscle tumors [14–18]. Mutation and overexpression of p53 have been described in a significant minority of uterine LMSs (25-47%) but not in leiomyomas [14, 17, 18]. Overexpression of p16 has been described in uterine LMSs and may prove to be a useful adjunct immunomarker for distinguishing between benign and malignant uterine smooth muscle tumors [12–14]. Overall, uterine LMS is a genetically unstable tumor that demonstrates complex structural chromosomal abnormalities and highly disturbed gene regulation which likely reflects the end-state of accumulation of multiple genetic defects. In comparison with other more common uterine malignancies, uterine LMSs bear some resemblance to type 2 endometrial carcinomas and high-grade serous carcinomas of ovary/fallopian tube origin, based on their genetic instability, frequent p53 abnormalities, aggressive behavior, and resistance to chemotherapy.

Expression and role of the luteinizing hormone/human chorionic gonadotropin (LH/hCG) axis in extragonadal tissues

It is not yet clear the role of ovarian stimulation in the development of uterine sarcomas. The presence of LH/hCG-Rs was shown for the first time by Reshef *et al.* [20] in the uterus of nonpregnant women by immunohistochemistry, an observation subsequently confirmed using different techniques [21, 22]. By acting through the transduction mechanisms described above, LH and hCG regulate ovarian steroidogenesis, but have also been shown to exert various effects on nongonadal tissues, such as endometrium, myometrium, and fallopian tubes. LH/hCG-Rs have been identified in epithelial and stromal cells of the endometrium, as well in smooth muscle cells of myometrium and uterine vessel. The expression of LH/hGC-R varied during the women's cycle phase, with the maximal expression occurring during the luteal phase [23]. Specific receptors for LH/hCG have also been identified in the myometrium of several animal species, including humans [24]. In this tissue, LH/hCG apparently acts through the LH/hCG-R-dependent activation of both the c-AMP and phospholipase C transduction pathways [24, 25]. It was proposed that the triggering of adenyl cyclase could determine an activation of COX-2, which in turn should induce an increase of the synthesis of either prostaglandin (PG)E, with an ensuing muscle relaxation, or PGF, which determines the contraction of the uterine musculature [26].

Conclusion

In the authors' opinion, it does not seem possible to verify the transition of a leiomyoma into a LMS in clinical practice so it cannot be established how unusual such event is and within what lapse of time it can appear. The case reported here is meant to underline the need to keep all uterine myomas, including when small in size, under control. Being able to find markers to predict the malignant potential of these neoplasms will be highly beneficial, in order to reach a consensus on their diagnosis and be able to manage them appropriately. Further studies are required to increase the validity of the current literature and add more knowledge on the subject. The oncogenic mechanisms underlying the development of uterine LMSs remain elusive.

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