Endometrial cancer: hidden pathology in a patient with abnormal uterine bleeding and known leiomyoma

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Established facts:

1. Endometrial cancer is the most common gynecological malignancy in the Western world
2. Endometrial sampling is an important assessment in older reproductive-aged and post-menopausal women with abnormal uterine bleeding

Novel insights:

1. Sampling the endometrium warrants consideration in women with known leiomyoma and abnormal uterine bleeding, regardless of planned treatment, especially with the trend toward conservative management of leiomyomas

Abstract

Uterine leiomyomas and endometrial pathology are both associated with abnormal uterine bleeding. We report a case in which a nulliparous woman with heavy uterine bleeding and leiomyomas had undergone two prior hysteroscopic myomectomies for benign leiomyomas. She was evaluated, but was ineligible for a clinical trial of a novel Magnetic Resonance guided High Intensity Focused Ultrasound (MRgHIFU) device. The 8 cm, prolapsed submucosal leiomyoma hindered endometrial sampling and was inaccessible to HIFU treatment. Preoperatively, neither endometrial sampling nor saline sonohysterography were technically feasible. She underwent hysterectomy, and on histological examination of specimen, stage 1A grade 1 endometrial carcinoma was found on the endometrial side of the prolapsing fibroid. Endometrial pathology is an important consideration in evaluation of abnormal uterine bleeding, even in women with large prolapsing leiomyoma.

Introduction

An estimated 200,000 hysterectomies are performed annually in the United States in women with uterine leiomyomas for symptoms of abnormal uterine bleeding, pelvic pain, and pressure symptoms on other structures such as urinary frequency, constipation or other changes in bowel function [1]. Developing an effective non-surgical treatment that spares the uterus and minimizes morbidity and mortality associated with myomectomy or hysterectomy has been an important priority. In particular, leiomyoma-associated infertility and miscarriage may ultimately be treated without altering hormonal or uterine function through minimally-invasive treatment such as Magnetic Resonance guided - High-Intensity Focused Ultrasound (MRgHIFU). As with medical treatments, MRgHIFU enables the woman to preserve her uterus and may additionally enable her to attempt pregnancy. In working towards non-surgical treatments, abnormal uterine bleeding observed with leiomyoma may warrant

additional investigation, especially in those over 35 years or with risk factors which suggest potential malignancy.

Case Report

A 41-year-old woman was evaluated for participation in a study using MRgHIFU for ablation of uterine leiomyoma (ClinicalTrials.gov Identifier: NCT00837161) [2]. She was diagnosed with uterine leiomyoma 7 years earlier. She suffered with menorrhagia, with prolonged bleeding between 10 and 17 days, and dysmenorrhea. She had undergone a hysteroscopic myomectomy and remained asymptomatic for a year and a half. However, she then presented with the same symptoms together with frequent urination and pelvic pressure. A second hysteroscopic myomectomy was performed after which she again was asymptomatic for a year and a half. Pathology reports for both surgeries indicated benign leiomyoma.

On presentation for study participation, she reported recent cycles ranging from 19 to 90 days with flow lasting between 14 and 27 days. She reported vaginal discharge for one week, with no pain, itchiness or discomfort. The patient denied urinary tract symptoms and was not sexually active. She had no previous abnormal Papanicolaou smears, sexually transmitted diseases, virilising signs, and had never used the oral contraceptive pill. She had never attempted to conceive. There was no family history of gynecological disease.

On speculum exam, a large leiomyoma prolapsing through the cervix and a white odorless vaginal discharge were noted. Bimanual examination confirmed that the leiomyoma filled the pelvis and prolapsed into the upper vagina. Pelvic ultrasound showed a uterine leiomyoma in the posterior wall and lower uterine segment measuring about 8 cm with heterogeneous texture and calcifications (Figure 1A). A smaller 3 cm leiomyoma was noted in this region.

Endometrial thickness was 1.5 cm. Ovaries were of normal size and morphology. Magnetic resonance imaging (MRI) of the pelvis found a large, bilobed partially mineralized pedunculated submucosal leiomyoma measuring 8.9 x 10 x 10.1 cm, that had prolapsed into the cervical canal and upper vagina (Figures 1B and 1C).

The patient was ineligible for study participation because the submucosal leiomyoma was more than 5 cm in diameter with areas of calcification and could not be reached by the HIFU beam path. Additionally, we were unable to sample the endometrium to exclude endometrial pathology as the fibroid completely obstructed the cervical canal. Although there were less invasive options available such as vaginal myomectomy followed by curettage, the patient wanted definitive therapy and underwent abdominal hysterectomy by a gynecologic oncologist (AS). Because the cervix was dilated and effaced, surgery required wide mobilization of the ureters in a manner analogous to a radical hysterectomy. On histologic examination of the uterus post-hysterectomy, a well-differentiated endometrial adenocarcinoma was identified on the endometrial side of the prolapsed fibroid. The depth of myometrial invasion was 5 mm within a total wall thickness of 22 mm. Although no formal staging was performed, no metastases were noted at the time of surgery or on reassessment of the pre-operative pelvic MRI and liver function tests. Based on the dimensions and histology grade, the patient had a stage 1A grade 1 endometrial cancer. In light of no evidence of metastasis, the low grade, small focus of endometrial cancer, and a low risk of metastatic disease to the adnexa (<5%), the patient did not want an early menopause and opted not to undergo oophorectomy.

Discussion

Our report illustrates a case of an occult endometrial cancer in a woman with a large, submucosal prolapsing leiomyoma. Endometrial cancer is the most common gynecological malignancy in the Western world [3], and the incidence increases over the age of 35 years and in women with unopposed estrogenic stimulation. This case highlights the importance of considering the differential diagnosis of uterine bleeding and the need for endometrial assessment particularly in women with abnormal uterine bleeding over this age. Our patient had some risk factors for developing endometrial cancer including early menarche, nulliparity, possible polycystic ovarian syndrome, and oligomenorrhoea. Twenty to twenty-five percent of cases occur in premenopausal women who may present with menorrhagia. A recent study found that pre-menopausal women with known leiomyoma have an even higher risk of endometrial cancer [4], highlighting the importance of assessing this sub-group in particular. While the first step may be transvaginal ultrasound, endometrial biopsy or dilatation and curettage enable histologic diagnosis.

The relationship between endometrial abnormalities and abnormal uterine bleeding may be considered in broad categories. In some, no endometrial abnormality may exist. For example, since submucosal fibroids or multiple intramural fibroids may theoretically create an increased endometrial surface area, heavy bleeding may result [5]. Similarly, heavy bleeding in the setting of anovulatory cycles does not always arise from endometrial abnormalities. In these circumstances, a blind biopsy of globally thick endometrium may provide a representative sample for diagnosis. However, focal endometrial abnormalities are most appropriately sampled using direct visualisation by hysteroscopy [5]. Considering when endometrial biopsy is warranted in the setting of abnormal bleeding aids the approach to diagnosis and treatment. Importantly, endometrial biopsy may not consistently predict

endometrial cancer. The risk of having cancer at surgery was higher when benign histology was noted on endometrial biopsy (45%) compared to pre-operative dilatation and curettage (30%) [6], perhaps due to the often focal nature of endometrial carcinoma [5].

Our study population were women with menorrhagia attributed to leiomyomas. Our patient was 41 years old, nulliparous, had menorrhagia, and was status post two prior hysteroscopic myomectomies which had not shown abnormal histology. The inability to sample the endometrium coupled with the fibroid characteristics of a large, calcified, prolapsing, sub-mucosal fibroid rendered the patient ineligible for HIFU.

Transvaginal ultrasound (TVS) is an effective tool in determining the endometrial thickness in women with heavy uterine bleeding. A thin endometrial echo on TVS (4mm or less) has a malignancy risk of 1 in 912 and so biopsy is not needed [5]. However, sonography may be difficult to perform or interpret in the setting of obesity, previous surgery and co-existing fibroids. Saline sonohysterography may then improve visualization of the endometrial cavity, enable differentiation among various endometrial findings (no anatomic pathology, globally thickened endometrium and focal abnormalities) and guide an approach to assessment. Sonographic assessment does not take the place of a tissue diagnosis but may be helpful in women with co-morbidities that hinder taking a tissue sample [7]. Due to the prolapsing fibroid, saline sonohysterography was not possible in this patient.

In conclusion, this report highlights the importance of considering endometrial pathology in patients with submucosal leiomyoma, even those with prior resection of benign, symptomatic submucosal leiomyoma. Endometrial cancer and fibroids are both common. Thus, they may be coincident or may be associated with each other, although no causal link has been reported.

HIFU is an emerging non-invasive technique for the treatment of uterine fibroids. With the trend toward conservative treatment of fibroids and non-invasive techniques, this case underscores the potential importance of endometrial sampling in women with fibroids, regardless of planned treatment.

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Contribution to authorship:

Dr Stratton: gynecologist responsible for the care of the patient described in the report and has directed and supervised the writing of the manuscript.

Dr Sri: compiled the clinical data and drafted the manuscript.

Dr Steren: gynecologist responsible for some of the care of the patient and provided critical review and revision of the manuscript.

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250 Legends:

251 Figure 1A: Transvaginal ultrasound image of the uterus in the sagittal plane, arrow
252 demonstrating a large pedunculated leiomyoma.

253 Figure 1B: T-2 Fat saturated MR image of the pelvis in the coronal plane, arrow
254 demonstrating a large pedunculated submucosal leiomyoma prolapsing into the
255 cervical canal and upper vagina

256 Figure 1C: T-2 Fat saturated MR image of the pelvis in the sagittal plane, arrow
257 demonstrating the prolapsing submucosal leiomyoma

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