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Gonadotropin-Releasing Hormone agonist Use in Adolescents with Uterine Leiomyomas

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1. ABSTRACT

1.1. Background: Uterine smooth muscle tumors are rare in adolescents (<21 years of age). This case report and review of literature discusses the use of Gonadotropin-Releasing Hormone (GNRH) analogues in adolescent patients with leiomyoma.

1.2. Case: A 14-year-old female presented with lower back pain and a uterine mass. MRI demonstrated a 10 cm mass arising from the anterior uterine wall, diagnosed by biopsy as a probable leiomyoma. She was treated with two doses of depot Lupron (a GNRH analogue), but this failed to decrease the mass. Incidentally, the patient was born with a meningomyelocele and as a result, had urinary incontinence and difficulty with ambulation. Options were discussed with the family and patient. Removing the mass would have removed the anterior wall of the uterus and closure was not believed possible. Furthermore, the mass failing to respond to the GNRH analogue made the diagnosis of a benign mass questionable. At the family's request, the patient underwent a hysterectomy; final pathology was consistent uterine leiomyoma.

1.3. Conclusion: This case and a review of the literature finds that response of uterine leiomyoma in adolescent patients to GNRH agonists is variable. These leiomyomas may not be hormonally-sensitive or may have a pathological basis that is different from the more common leiomyoma in older women.

2. INTRODUCTION

Uterine leiomyomas are common benign neoplasms and are distinguished from other Smooth Muscle Tumors (SMT), such as uterine Leiomyosarcomas (LMS) and uterine Smooth Muscle Tumors of Uncertain Malignant Potential (STUMP), by pathological and molecular features [1]. Differentiation of malignant potential is difficult in all age groups. Imaging, such as ultrasound, CT scan and MRI can assist in defining characteristics of the mass. MRI may identify features of LMS such as irregular contours, heterogenous and increased signal intensity, and can distinguish leiomyomas from LMS in many cases. Yet, MRI may not be able to discern a LMS from a degenerated leiomyoma or STUMP, for example [2,3].

The use of Gonadotropin-Releasing Hormone (GNRH) agonists prior to surgical resection is common in adult patients [4]. Continuous dosing (as opposed to pulsatile dosing) of GNRH agonists leads to ovarian suppression and decreased ovarian estrogen production [5]. In adult, pre-menopausal patients, GNRH agonists have been shown to decrease the size of leiomyomas by up to 77% [4-6]. Studies have found that a reduction in size of the mass after treatment with GNRH agonists also can support the diagnosis of benign leiomyoma over that of LMS or STUMP [7].

Only a few cases of the use of GNRH agonists in the management of leiomyoma in young patients have been reported [7-9]. Our case illustrates dilemmas faced in the management of a large uterine mass in an adolescent patient and the limitations of GNRH agonist therapy.

3. CASE

A 14-year-old female presented with back pain. She was born with a meningomyecele and an Arnold Chiari Malformation. She had resultant urinary retention requiring self-catheterization and ambulatory difficulty. Her menstrual history included menarche at age twelve years and a six-month history of heavy menstrual bleeding. Her abdomen was non-tender, non-distended, and there was a firm, approximately 10 cm mass felt in the lower abdomen. Pelvic exam was deferred. CT scan found a 10.0 cm by 9.2 cm by 8.5 cm uterine mass. Pelvic ultrasound noted bilateral hydronephrosis. Baseline labs revealed a low hemoglobin (10.1 g/dL), normal platelet count, normal lactate dehydrogenase, and normal liver and renal function. MRI confirmed the presence of a large solid mass that appeared to arise from the anterior uterine myometrium (Figure 1).

An exploratory laparotomy was performed. The mass was smooth and appeared benign, originating from the anterior surface of the uterus. Multiple core biopsies were obtained. Histology was reported as low-grade/ benign smooth muscle mesenchymal neoplasm (leiomyoma). Positive tumor markers included desmin, smooth-muscle actin, and muscle-specific actin. Diffuse nuclear positivity for estrogen, progesterone, and WT1 was also observed. Whole genome, whole exome, and transcriptome analysis showed a rearrangement between *RAD51B* and *SMIM29* genes, moderately high expression of *HMGA1* gene, and interstitial deletion in 1p, all indicating the tumor was likely benign.

However, the mass was symptomatic and causing bilateral ureteral obstruction. Imaging indicated that resection at this time would not be possible without removing most of the anterior uterine wall or necessitating a hysterectomy.

The decision was made to administer a GNRH agonist in hopes of reducing the size of the tumor and preserving the uterus with a future surgery.

An intramuscular injection of leuprorelin (Lupron Depot) 11.25 mg was administered; however, no decrease in size was noted on exam or by MRI at 2 months. A second injection was administered at 3 months and repeat MRI at 4 months revealed a slight increase in size; no apparent plane was noted between the mass and the uterus itself, and the patient's symptoms persisted. Due to the tumor's growth while on GNRH agonist therapy and the concern for malignant potential, it was decided to proceed with complete surgical resection of the mass. Options were discussed with the family and patient. Removing the mass would have removed the anterior wall of the uterus and closure was not believed possible. Furthermore, the mass failing to respond to the GNRH analogue made questionable the diagnosis of a benign mass. At the family's request, the patient underwent definitive surgery.

Intraoperatively, laparoscopic inspection confirmed that a myomectomy would not be possible without removing the entire anterior wall of the uterus. A hysterectomy and bilateral salpingectomy were undertaken. Final pathology of the mass was consistent with the initial diagnosis of uterine leiomyoma. Stained sections demonstrated a predominately intramural, well-demarcated mesenchymal neoplasm with no cytological atypia or areas of necrosis. The patient's postoperative course was uneventful.

Table 1: GNRH Agonist Treatment of Uterine SMT in Adolescents.

Author	Patient age (years)	Presenting symptoms	Tumor size (cm) before treatment	Treatment regimen	Tumor response in volume	Final Diagnosis
Murry et al. (index case) N = 1	14	Lower back pain	10.2 cm × 9.6 cm × 8.5 cm	Leuprorelin 11.25 mg, every 3 months × 2 doses	Increased	Leiomyoma
Hughes et al. [7] N=1	20	HMB*, bloating, urinary frequency	Not informed	Gosarelin 3.60 mg, every 4 weeks × 6 doses	Decreased	STUMP
Maggiore et al. [8] N=1	14	HMB*, abdominal and back pain	15 cm × 13 cm × 10 cm	Leuprorelin 3.75 mg, 1 dose	Decreased	Leiomyoma
Tsakiridis et al. [9] N=1	19	Pelvic pain, HMB*, urinary frequency	12 masses of different sizes (up to 4 cm)	Triptorelin 3.75 mg, every 4 weeks × 6 doses	No response	STUMP

HMB*, heavy menstrual bleeding

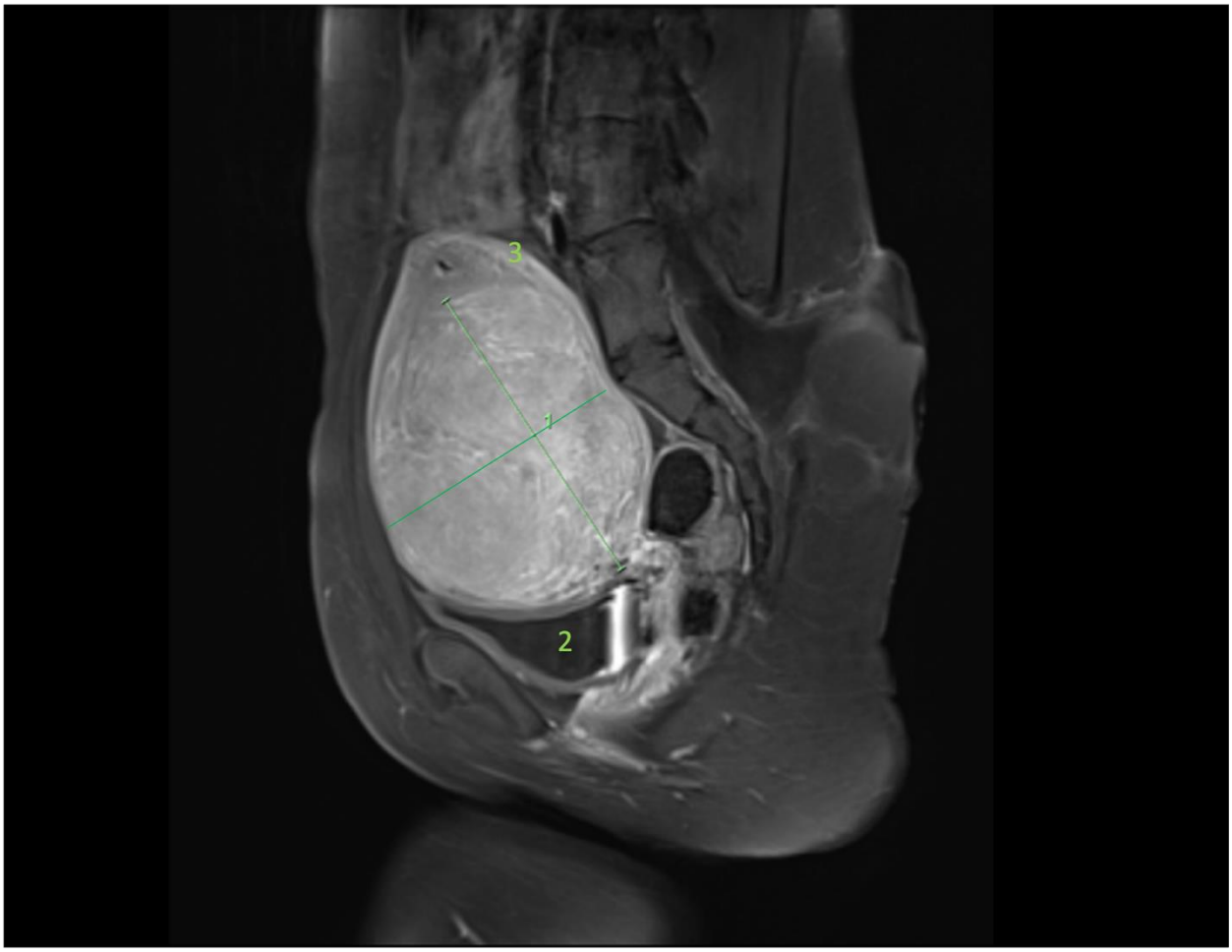

Figure: Sagittal T1-weighted MRI showing a 10.2 x 9.6 x 8.5 cm avidly enhancing, solid mass that appeared to arise from the anterior uterine myometrium.

Legend: 1 mass, 2 bladder, 3 uterine myometrium

4. DISCUSSION

Our case of a 14-year-old with a large uterine leiomyoma demonstrates challenges in diagnosis and management. The benign mass did not respond to GNRH agonist therapy as would have been predicted and in fact, it grew under observation. Concern for malignancy as well as symptomatology required definitive surgery.

A search of the English language literature was conducted using search terms: fibroids, uterine leiomyoma, smooth muscle tumors of the uterus, with adolescents, age <21 years, gonadotropin-releasing hormone agonist. In addition to the index case, 3 reports of patients less than 21 years of age with presumed benign leiomyomata who were treated with GNRH analogues were found (Table 1). In 2 cases [7,8] the mass decreased in size, and in one case [9], there was no change in size. One case had a final diagnosis of STUMP and yet responded to GNRH analogue

treatment [7]. In our case, the final pathology had benign findings, but the mass increased in size over a 5 to 6 months period. Other features of the cases are described in the Table 1.

The prevalence of uterine leiomyoma in adolescents ages 15 to 19 years is estimated to be 0.4% [10]. There are no specific guidelines for treatment of uterine leiomyomas in adolescents [11]. Moroni et al. reviewed 19 cases of leiomyomas in adolescents ages 15 to 18 years [12]. Similarly, to our case, abnormal uterine bleeding and abdominal pain were the most common symptoms and a pelvic mass was the most common finding. Most (16 of 19) were managed with myomectomy; no cases were noted to have been managed with GNRH analogues. Murphy, et al. added a few more cases to the list; only 5 patients total were aged 12 to 15 years [11]. None were managed with a GNRH agonist and most underwent a myomectomy for treatment. However, Khaja, et al reported a 10-year-old girl who presented with excessive menstrual bleeding and a biopsy of a 2 cm uterine mass found a "possible leiomyoma" [13]. A regimen of Depot Lupron was given for 6 doses. Bleeding persisted and another laparoscopic-directed biopsy found a likely adenomyoma. A levonorgestrel-containing IUD was placed, and the bleeding was controlled. This case was not included in our series because the final diagnosis was unclear.

Continuous dosing of GNRH agonists works to decrease the size and mass of leiomyoma by inhibiting the pituitary's secretion of Luteinizing Hormone and Follicular Stimulating Hormone, thereby suppressing ovarian estrogen and progesterone production [14]. Changes in blood flow as a result cause leiomyoma to shrink [15]. Another theory is that GNRH agonists reduce growth hormones and cytokines that support the growth of uterine leiomyoma [16]. That uterine leiomyoma in very young patients do not respond typically to GNRH agonists seems to indicate that they may not be hormonally-sensitive and may have a pathological basis that is different from the more common leiomyoma in older women.

In conclusion, our case and the review of literature found that GNRH analogue use has only rarely been reported in the management of leiomyomas in young patients, and results are variable. Moreover, their value in predicting malignant potential appears to be limited. Further research is warranted.

5. DECLARATION

This study was reviewed and approved by the IRB of St. Jude Children's Research Hospital. IRB Number: 23-1320; Mnemonic: LLSTUMP. Reference Number: 021558 Project Title: Leiomyomas, leiomyosarcomas, and uterine smooth muscle tumors of uncertain malignant potential: A Case Report Submission Type: Non-Human Subjects Research Determination.

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