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Aromatase inhibitor treatment of menorrhagia and subsequent pregnancy in a patient with Familial Hyperparathyroidism-Jaw Tumor Syndrome

Erin F. Wolff, MD[1,2], **Micah J. Hill, DO**[1], **William F. Simonds, MD**[3], and **James H. Segars, MD**[1]

[1]Program in Reproductive and Adult Endocrinology, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, USA

[3]Metabolic Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland, USA

Abstract

Objective—To describe the clinical management of menorrhagia in a woman with Hyperparathyroidism-Jaw Tumor Syndrome (HPT-JT).

Design—Case report.

Setting—Large translation research hospital.

Patient—A 26 year old nulligravid woman with familial HPT-JT presented with life-long menorrhagia resistant to progesterone IUD therapy and a desire for fertility.

Intervention—Aromatase inhibitor therapy.

Main Outcome Measures—Clinical response to therapy and pregnancy.

Result—Imaging demonstrated an enlarged endometrial lining and thickening of the junctional zone. At operative hysteroscopy, multiple atypical endometrial polyp-like lesions filled the entire uterine cavity and were removed. Histologic evaluation demonstrated the lesions to be adenomyomas with an abundance of aromatase expression. Postoperative treatment included an aromatase inhibitor. The patient's menorrhagia, which had previously been resistant to progesterone IUD therapy, resolved with the aromatase inhibitor. After ten months of this treatment, the aromatase inhibitor was discontinued and a repeat hysteroscopy revealed a markedly improved uterine cavity. The patient subsequently became pregnant on her first natural cycle and delivered a healthy term infant.

Conclusion—Aromatase inhibitors may represent a novel treatment for benign uterine pathology in HPT-JT.

[2]Corresponding author: Erin F Wolff, address: National Institutes of Health, CRC Rm 1E-3140, 10 Center Drive Bethesda, MD 20892, wolffe@mail.nih.gov, phone: 301-496-5800.

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Keywords

hyperparathyroidism-jaw tumor syndrome; menorrhagia; adenomyoma; aromatase inhibitor

Introduction

The Hyperparathyroidism-Jaw Tumor Syndrome (HPT-JT) is a rare autosomal dominant syndrome resulting from loss-of-function mutation in the gene *CDC73/HRPT2* (1). The product of the gene is parafibromin, a ubiquitously expressed protein and a putative tumor suppressor (2, 3). Parafibromin has both nuclear and nucleolar localization signals and the L95P missense mutation described in our case study causes loss of nucleolar localization which may result in dominant interference causing enhanced cell cycle progression and increased cell survival (4). Germline mutations in *CDC73/HRPT2* resulting in loss of parafibromin function predispose patients to fibro-osseous jaw tumors and parathyroid tumors (2). Recently, it was noted that females with this disorder have decreased reproductive potential and a high prevalence of atypical uterine tumors (3) In addition, affected women experience profound abnormal uterine bleeding, which often results in hysterectomy in their thirties due to life threatening menorrhagia (3).

Case

A 26 year old nulligravida woman from a family with HPT-JT was referred for life-long menorrhagia resulting in anemia. Members of her family were known to carry a L95P missense mutation in *CDC73/HRPT2* (4), and several were affected with HPT-JT, including the patient's brother who had severe comorbidities from hyperparathyroidism. The patient had a medical history of hypertension since the age of ten, subclinical hypothyroidism, and hyperprolactinemia from a microprolactinoma. She had previous treatment of her microprolactinoma with cabergoline, which was subsequently discontinued. At presentation to our clinic, she was not on medication for hyperprolactinemia, had normal prolactin levels and a stable 3mm pituitary adenoma on MRI imaging. Biochemical screening showed no evidence of hypercalcemia or hyperparathyroidism. She had prior surgical removal of a large, benign polyp prolapsing through the cervix. The patient desired management of her menorrhagia and the ability to conceive. She had a progesterone intrauterine device in the uterus on presentation. She was seen under an institutional review board approved research protocol at the National Institutes of Health and signed written, informed consent. The patient was genotyped and found to be heterozygous for a germline L95P parafibromin missense mutation.

Materials and Methods

Transvaginal ultrasonography was performed with a Voluson E6 (General Electric,Fairfield, CT). Surgical specimens obtained at hysteroscopic resection were fixed and paraffin embedded. Serial sections were reacted with Anti-Aromatase antibody (Abcam ab35604). Staining for aromatase was performed in a control endometrial biopsy and endometrial tissue from the case patient resected at surgery.

Results

Physical examination was notable for a large everted external cervical os. Transvaginal ultrasound and magnetic resonance imaging demonstrated an enlarged endometrial lining with thickening of the junctional zone (Figure 1). The cervix had multiple cystic structures and was enlarged to the size of the uterine corpus. Operative hysteroscopy revealed a uterine

cavity filled with atypical, fibrous endometrial polyp-like structures which extended from the fundus and down through the cervix (Figure 2). The largest lesion was 15mm. The polyps were surgically removed with electrocautery and multiple mucous filled cysts were seen which extruded “chocolate like” material on cauterization. Due to the extensive nature of the polypoid structures, not all of them could be removed and sharp curettage was performed. Histologic examination of these polypoid structures revealed benign uterine adenomyomas. A new progesterone IUD was placed in the uterine cavity in the operating room for management of menorrhagia.

Five months later the patient presented with persistence of menorrhagia. Special staining for aromatase was then performed on her histologic tissue samples from the prior surgery. This staining revealed an over-expression of aromatase within her adenomyomas as compared to normal controls without adenomyomas (Figure 3). The patient was started on an aromatase inhibitor (Letrozole 2.5 mg/day). The patient received transvaginal ultrasound monitoring every three months. At each monitoring appointment the ovaries were normal in appearance without the formation of cystic structures. Upon follow up six months after the aromatase inhibitor was started, the patient noted decreased uterine bleeding and her endometrial lining was thin at 4mm.

Post-operatively, the patient received medical therapy with an aromatase inhibitor and a progesterone intrauterine device. This treatment was continued for a total of ten months resulting in continued improvement in her symptoms. The patient desired pregnancy and a follow-up hysteroscopy documented dramatic improvement in the uterine cavity with a few smaller polyps the largest of which was 3mm. The IUD and the remaining small polyps were surgically removed. The aromatase inhibitor was discontinued three months after surgery and the patient became spontaneously pregnant with her next ovulatory cycle. She had an uncomplicated pregnancy resulting in a term spontaneous vaginal delivery of a 4479gm female.

Discussion

Parathyroid tumors resulting in hyperparathyroidism are the typical presenting manifestation and occur in some 90% of patients with HPT-JT (5). Ossifying jaw tumors occur in ~35% of patients and less prevalent features include renal tumors and cysts (3). Only recently it has been recognized that this syndrome is also associated with a spectrum of uterine disease. This was first described in a report of two sisters who with HPT-JT who both had uterine adenomyomatous polyps similar to those describe in this case report (6). In the largest case series of women with HPT-JT, 31 of 39 women from 13 families had menorrhagia leading to hysterectomy at a mean age of thirty-five years (3). Of patients in whom histologic specimens were available for review, there were eight cases of extensive adenomyosis, five adenofibromas, four leiomyomas, four endometrial hyperplasia, and two adenosarcomas (3). The tumors were noted to derive from a common embryologic origin of mesodermal Mullerian tissue. Females with HPT-JT were more likely to be childless as compared to their unaffected female siblings (27% versus 3%, $p<0.001$) (3). Furthermore, affected females were significantly more likely to be childless as compared to their affect male siblings (27% versus 4%), suggesting the increased childlessness is these affected families occurred in females but not males (3). Subsequent case series have confirmed the association of HPT-JT syndrome and uterine tumors, with uterine pathology occurring in 33-79% of affected females (7-10). It is unclear whether the decreased offspring seen in affected females is the direct result of early hysterectomy or related to infertility or miscarriage from the uterine pathology itself. These observations demonstrate the significant pathology of HPT-JT on the female reproductive tract and reproductive potential.

To our knowledge, assessment of aromatase expression in the uterine pathology of HPTJT has not been reported. Aromatase and 17-hydroxysteroid dehydrogenase have been demonstrated to be overexpressed in leiomyoma as compared to normal myometrial tissue (11). This raises a potential mechanism by which local conversion of androgens to estrogens is involved in the growth of leiomyomas, a mechanism supported by the observation that hypoestrogenic states are typically associated with a decrease in leiomyoma size (11). Treatment with aromatase inhibitors has been shown to decrease leiomyoma volume and increase hematocrit (12,13).

The data showing increased aromatase expression in leiomyomas led us to evaluate the aromatase expression in the histologic adenomyoma specimens from this patient. Testing for somatic DNA changes and aberrant protein expression in the uterine tumors of HPT-JT patients in an important next step in understanding the pathogenesis of these tumors (3). The finding of increased aromatase expression in this patient's adenomyomas led us to add an aromatase inhibitor to her medical treatment regimen. While her symptomatology had not improved after hysteroscopic resection and progesterone IUD therapy, the aromatase inhibitor therapy resulted in clinical improvement in her menorrhagia. Further, repeat hysteroscopy revealed a markedly improved uterine cavity with the presence of only a few small lesions. Finally, the patient was able to immediately become pregnant after discontinuation of the therapy.

In an endometrial explant culture study, it was demonstrated that exposure of endometrial cells to androgens, specifically androstenedione, resulted in marked up-regulation of aromatase mRNA (5). The resulting increase in estradiol production induced expression of SF-1, which led to further activation of CYP19 promotor expression, and increased estradiol production. These results suggested a positive feed-forward mechanism of androgen to estradiol production resulting in increased survival and proliferation of endometrial cells. Aromatase inhibitors were shown to suppress the stimulatory effects of androstenedione, testosterone, and estradiol on aromatase mRNA (5). Disruption of this feed-forward loop may be beneficial decreasing local estradiol production and in disrupting the pathogenesis of endometrial diseases. In addition, blocking aromatization to estradiol would be expected to lead to an increase in local androgen levels, which may inhibit local cell growth and endometrial secretory activity (6). Aromatase inhibitors have also been show to decrease the expression of IGF-1, prostaglandin E, and vascular endothelia growth factor in both endometrial explants and myometrium, providing additional potential mechanisms by which local growth factors can be inhibited with aromatase inhibitor treatment (7).

Further study is needed to characterize the uterine tumors found in women with HPT-JT. In this case report, the use of aromatase inhibitors resulted in marked clinical improvement, decreased menorrhagia, and the ability to conceive. This may represent a novel therapy for the medical therapy of benign uterine lesions in women with HPT-JT.

Acknowledgments

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References

1. Carpten JD, Robbins CM, Villablanca A, Forsberg L, Presciuttini S, Bailey-Wilson J, et al. HRPT2, encoding parafibromin, is mutated in hyperparathyroidism-jaw tumor syndrome. Nat Genet. 2002; 32:676–80. [PubMed: 12434154]

2. Sharretts JM, Simonds WF. Clinical and molecular genetics of parathyroid neoplasms. Best Pract Res Clin Endocrinol Metab. 2010; 24:491–502. [PubMed: 20833339]
3. Bradley KJ, Hobbs MR, Buley ID, Carpten JD, Cavaco BM, Fares JE, et al. Uterine tumours are a phenotypic manifestation of the hyperparathyroidism-jaw tumour syndrome. J of Intern Med. 2005; 257:18–26. [PubMed: 15606373]
4. Panicker LM, Zhang JH, Dagur PK, Gastinger MJ, Simonds WF. Defective nucleolar localization and dominant interfering properties of a parafibromin L95P missense mutant causing the hyperparathyroidism-jaw tumor syndrome. Endocr Relat Cancer. 2010; 17:513–24. [PubMed: 20304979]
5. Bukulmez O, Hardy DB, Carr BR, Auchus RJ, Toloubeydokhti T, Word RA, et al. Androstenedione up-regulation of endometrial aromatase expression via local conversion to estrogen: potential relevance to the pathogenesis of endometriosis. J Clin Endocrinol Metab. 2008; 93:3471–7. [PubMed: 18559914]
6. Tuckerman EM, Okon MA, Li T, Laird SM. Do androgens have a direct effect on endometrial function? An in vitro study. Fertil Steril. 2000; 74:771–9. [PubMed: 11020522]
7. Kudoh M, Susaki Y, Ideyama Y, Nanya T, Mori M, Shikama H. Inhibitory effects of a novel aromatase inhibitor, YM511, on growth of endometrial explants and insulin-like growth factor-I gene expression in rats with experimental endometriosis. J Steroid Biochem Mol Biol. 1997; 63:75–80. [PubMed: 9449208]

Aromatase inhibitor therapy improved progesterone resistant menorrhagia in a patient with Hyperparathyroidism-Jaw Tumor Syndrome.

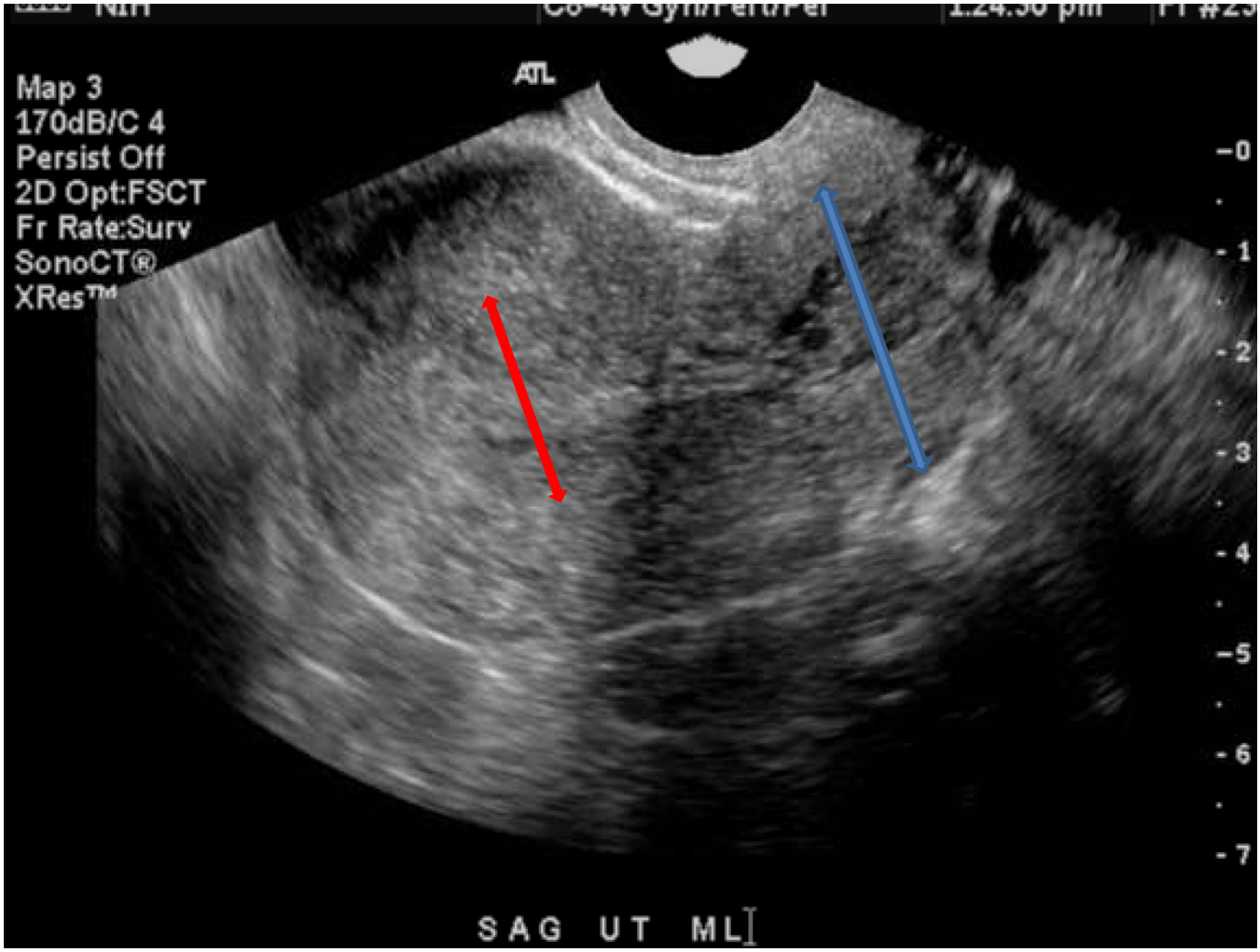

Figure 1.
Transvaginal ultrasound of the uterus (sagittal view) demonstrating a thickened endometrial lining (red arrow), increased junctional zone, and enlarge cervix (blue arrow) with multiple cystic structures.

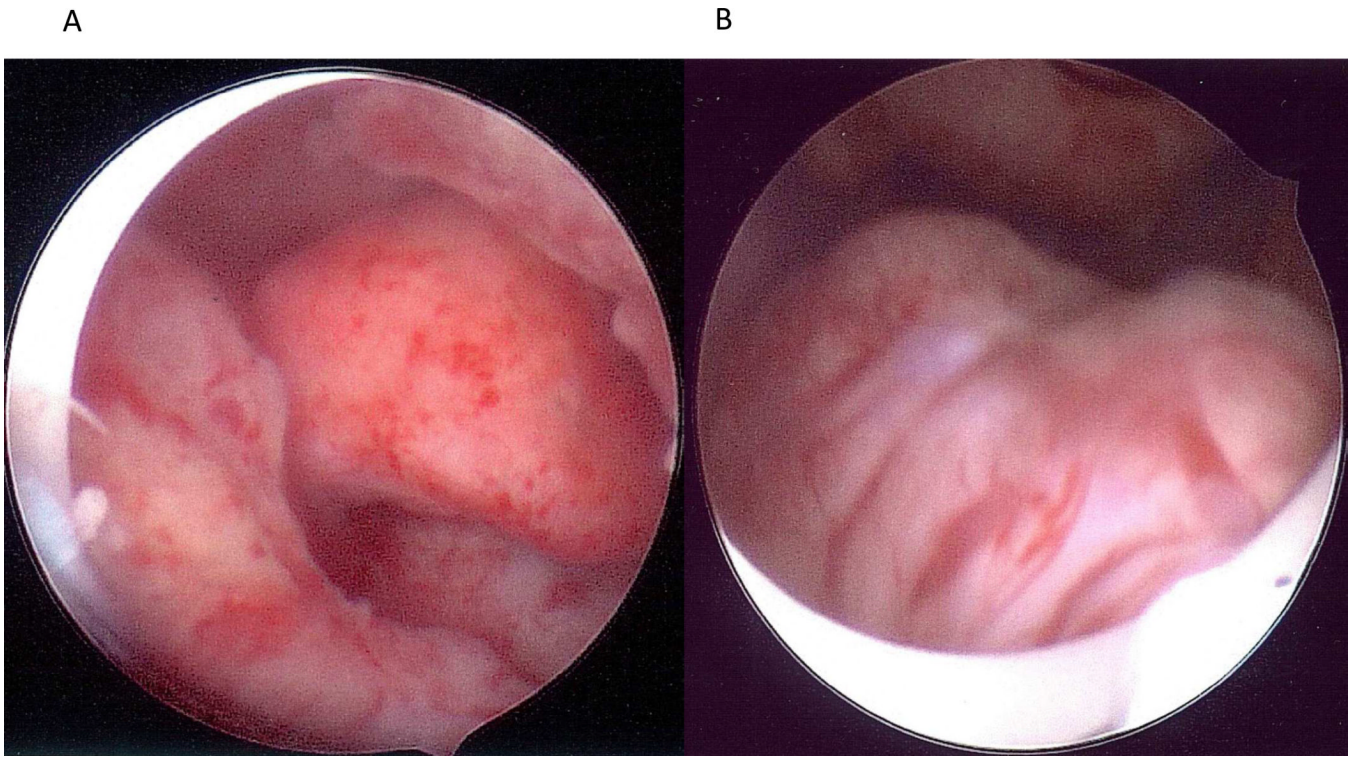

Figure 2.
Hysteroscopic view of the uterine cavity. Left (A) and Right (B) views revealed multiple adenomyomas measuring up to 15mm in size. Biopsy confirmed adenomyomas.

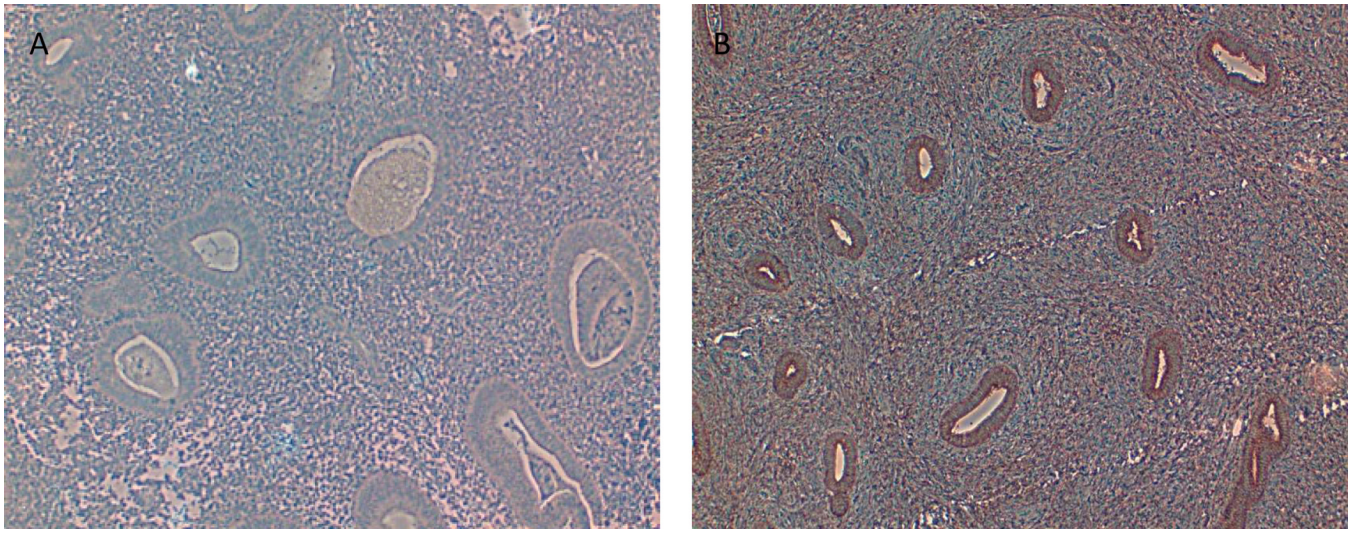

Figure 3.

Surgical specimens were fixed and paraffin embedded. Serial sections were reacted with Anti-Aromatase antibody (Abcam ab35604). Staining for aromatase in a control endometrial biopsy (left) and an endometrial adenomyoma resected at surgery (right). The right panel shows increased staining for aromatase in the mesodermal and glandular HPT-JT tissue.