Aromatase inhibitor treatment of menorrhagia and subsequent pregnancy in a patient with familial hyperparathyroidism–jaw tumor syndrome

Erin F. Wolff, M.D.,[a] Micah J. Hill, D.O.,[a] William F. Simonds, M.D.,[b] and James H. Segars, M.D.[a]

[a] Program in Reproductive and Adult Endocrinology, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development; and [b] Metabolic Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland

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(s): A 26-year-old nulligravid woman with familial HPT-JT presented with life-long menorrhagia resistant to progesterone intrauterine device (IUD) therapy and a desire for fertility.
Intervention(s): Aromatase inhibitor therapy.
Main Outcome Measure(s): Clinical response to therapy and pregnancy.
Result(s): 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 10 months of this treatment, the aromatase inhibitor was discontinued and a repeated hysteroscopy revealed a markedly improved uterine cavity. The patient subsequently became pregnant on her first natural cycle and delivered a healthy term infant.
Conclusion(s): Aromatase inhibitors may represent a novel treatment for benign uterine pathology in HPT-JT. (Fertil Steril® 2012;98:1616–9. ©2012 by American Society for Reproductive Medicine.)
Key Words: Hyperparathyroidism–jaw tumor syndrome, menorrhagia, adenomyoma, aromatase inhibitor

Discuss: You can discuss this article with its authors and with other ASRM members at http://fertstertforum.com/wolffef-menorrhagia-hyperparathyroidism-jaw-tumor-syndrome/

Use your smartphone to scan this QR code and connect to the discussion forum for this article now.*

* Download a free QR code scanner by searching for "QR scanner" in your smartphone's app store or app marketplace.

Received June 25, 2012; revised and accepted August 8, 2012; published online September 8, 2012.
E.F.W. has nothing to disclose. M.J.H. has nothing to disclose. W.F.S. has nothing to disclose. J.H.S. has nothing to disclose.
Supported in part by the Intramural Research Program of the Program in Reproductive and Adult Endocrinology, National Institute of Child Health and Human Development (Z01 HD008924-01 and Z01 ND008737-12), and the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health.
The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of the Army, Department of Defense, or the U.S. Government.
Presented at the Society for Gynecologic Investigation, San Diego, California, March 21–24, 2012.
Reprint requests: Erin F. Wolff, M.D., National Institutes of Health, CRC Rm. 1E-3140, 10 Center Drive, Bethesda, MD 20892 (E-mail: wolffe@mail.nih.gov).

Fertility and Sterility® Vol. 98, No. 6, December 2012 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2012.08.017

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 the present 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 female individuals 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 owing 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 10 years, 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 and had normal prolactin levels and a stable 3-mm pituitary adenoma on magnetic resonance imaging. Biochemical screening showed no evidence of hypercalcemia or hyperparathyroidism. She had earlier 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 (IUD) on presentation. She was seen under an Institutional Review Board–approved research protocol at the National Institutes of Health and signed a written informed consent. The patient was genotyped and found to be heterozygous for a germline L95P parafibromin missense mutation.

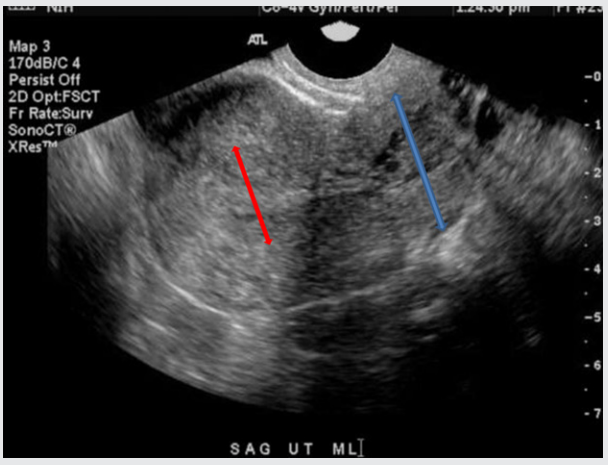
METHODS

Transvaginal ultrasonography was performed with a Voluson E6 (General Electric). Surgical specimens obtained at hysteroscopic resection were fixed and paraffin embedded. Serial sections were reacted with anti-aromatase antibody (ab35604; Abcam). Staining for aromatase was performed in a control endometrial biopsy, and endometrial tissue from the case patient was 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 (Fig. 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 (Fig. 2). The largest lesion was 15 mm. The polyps were surgically removed with electrocautery, and multiple mucus-filled cysts were seen which extruded "chocolate-like" material on

FIGURE 1



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

Wolff. Aromatase inhibitor for HPT-JT syndrome. Fertil Steril 2012.

cauterization. Owing 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 earlier surgery. This staining revealed an overexpression of aromatase within her adenomyomas compared with normal control samples without adenomyomas (Fig. 3). The patient was started on an aromatase inhibitor (Letrozole, 2.5 mg/d). The patient received transvaginal ultrasound monitoring every 3 months. At each monitoring appointment, the ovaries were normal in appearance without the formation of cystic structures. At follow-up 6 months after the aromatase inhibitor was started, the patient noted decreased uterine bleeding and her endometrial lining was thin, at 4 mm.

Postoperatively, the patient received medical therapy with an aromatase inhibitor and a progesterone IUD. This treatment was continued for a total of 10 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 3 mm. The IUD and the remaining small polyps were surgically removed. The aromatase inhibitor was discontinued 3 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 4,479 g girl.

DISCUSSION

Parathyroid tumors resulting in hyperparathyroidism are the typical presenting manifestation and occur in some 90% of