

## Effect of octreotide on endometriosis in acromegaly: Case report with review of literature

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### ABSTRACT

**Objective:** To study the effect of octreotide therapy on endometriotic lesions in a patient with coexisting endometriosis and acromegaly. **Intervention:** Patient: A 34-year-old female was diagnosed with acromegaly and coexisting endometriosis. Post-surgical resection of the tumor, patient was initiated on octreotide therapy. **Results:** There was improvement in menstrual bleeding as IGF1 levels decreased with Octreotide therapy. Resolution of the endometriotic lesions was observed during follow up. **Conclusion:** In this unusual case, the treatment of acromegaly concurred with regression in the endometriotic lesions. Causal or incidental association cannot be inferred from the present case.

**Key words:** Acromegaly, endometriosis, octreotide, remission of endometriosis

### INTRODUCTION

The hypothalamo-pituitary ovarian axis is commonly affected in patients with acromegaly. The various gonadal dysfunctions range from oligo-amenorrhea, infertility to menopausal symptoms including hot flushes and vaginal atrophy.<sup>[1-3]</sup> Uncommonly, acromegalic females may present with features of PCOS i.e. hirsutism, menstrual disturbances and polycystic ovaries.<sup>[4]</sup> Causes of ovarian dysfunction in these patients include hyperprolactinemia, gonadotropin dysfunction due to pituitary mass effect and direct or indirect effect of Growth Hormone (through Insulin like Growth factors) on ovaries.<sup>[1]</sup>

Endometriosis is a chronic and recurrent disease characterized by the presence and proliferation of endometrial tissue outside the uterine cavity, which occurs in

approximately 10% of women of reproductive age.<sup>[5]</sup> This is estrogen dependent disorder, whereby lesions respond to inhibition of gonadotropin pulses by GNRH analogues or decrease in estrogen production by aromatase inhibitors.<sup>[6-9]</sup> To the best of our knowledge, this condition has never been reported in patients with acromegaly earlier. We report a case of a 34 year old female, with endometrisois who was diagnosed with a GH secreting tumor. The endometrial lesions gradually regressed over time as the acromegaly was treated. The possible reasons for this are discussed.

### CASE REPORT

A 34-year-old female presented in the gynaecology outpatient department with complaints of menorrhagia and passage of clots along with abdominal pain which she had been experiencing for the last 13 years. Periods had been regular otherwise, lasting for about 5-6 days each month. USG pelvis revealed bilateral complex cystic adnexal masses with diffuse low level internal echoes. The left adnexal cyst was larger (6.5 × 6.0 cm) and multiloculated. The right adnexal cyst was unilocular and of size 3.5 × 2.8 cm [Figure 1]. MRI pelvis was done subsequently which revealed bilateral cysts, hyperintense on T1 and T1 fat suppressed images and hypointense with

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few hyperintense areas (shading) on T2WI and a diagnosis of endometriotic cysts was made [Figure 2a and b]. She was advised to take oral contraceptives and NSAIDs. There was however no change in either the menstrual flow or clots with this therapy. She discontinued the therapy after two months.

Three months later, she approached the doctor with additional complaints of diplopia and left sided temporal hemianopia. MRI brain was done, this revealed a pituitary macroadenoma. She was then referred to the department of Endocrinology for further assessment and management of macroadenoma. History and clinical features were suggestive of acromegaly. Post glucose load Growth Hormone levels were high (39.8 ng/ml). Prolactin levels were 70 ng/ml and freeT4 levels were low (freeT4-0.60 ug/dl (0.6-2.2), TSH-4.410 mIU/ml). Thyroxine supplementation was initiated. The patient underwent pituitary surgery, five months following which she underwent 25 sessions of radiotherapy (SRT). Menstrual problems persisted and she underwent dilatation and curettage followed by biopsy of the

endometrium which was suggestive of endometrial hyperplasia.

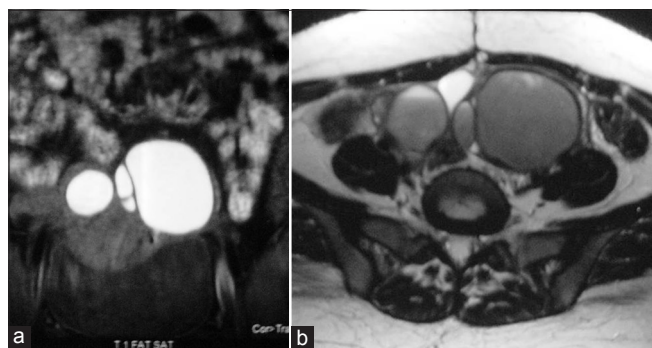
As her IGF-1 levels were high even nine months post operatively, the patient was put on Injection Octreotide. (IGF1-710:Nomalrange 117-329  $\mu\text{g/L}$ ). Six months from the introduction of octreotide, the patient developed gallstones. During this period, the patient's menstrual flow had decreased from 5 to 3 days and there was a reduction in the amount of clots. Follow up ultrasound scans revealed a significant decrease in the size of the lesions over a period of one year with bilateral normal ovaries in the scans done at three years and subsequently [Figure 3]. She was continued on monthly octreotide injections. There was a gradual decline and normalisation of IGF-1 levels over a period of three years with this treatment [Table 1]. Octreotide therapy was stopped after four years. Concurrently, there was a gradual improvement and normalisation of menstrual flow and pattern. Ultrasonography revealed bilateral normal ovaries. Presently, the patient is amenorrhoeic for the past 3 years. Hormonal profile was suggestive of hypogonadotrophic hypogonadism (LH-1.84 mIU/ml normal value range 0.8-15.5 mIU/ml in fertile females age group, FSH-7.03 mIU/ml normal value range 1.3-23.4 mIU/ml, E2-3.00 pmol/L (97.5-592 pmol/L), Progesterone -0.052 (0.44-6.47 nmol/L), Prl-15.2 ng/ml, normal value range 3-18.6 ng/ml.

## DISCUSSION

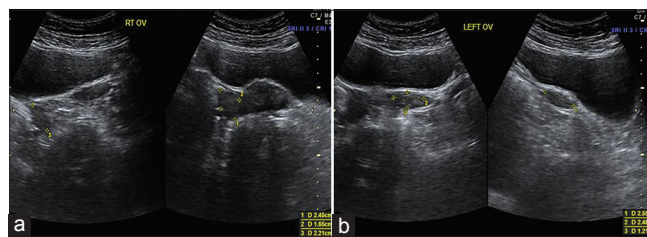
Endometriosis is a gynaecological disease with endometrial tissues growing at extra uterine sites, most commonly ovaries, other sites being pelvic peritoneum, vagina, bowel, pericardium, sites of previous surgical incisions and least commonly lungs and pleura.<sup>[5]</sup> Signs and symptoms may range from dysmenorrhea, pelvic pain to infertility. It usually occurs during the reproductive age and prolonged periods of unopposed estrogen and fewer pregnancies may predispose women to endometriosis. The symptoms and lesions of endometriosis regress with reduction of estrogen levels as in surgical, hormonal or natural menopause.<sup>[5,10]</sup> An increased risk (5-8%) amongst the first degree relatives, an



**Figure 1:** TAS shows bilateral complex cystic adnexal masses with diffuse low level internal echoes. Left adnexal cyst is larger and multiloculated



**Figure 2:** (a) Coronal T1 fat suppressed MR image shows bilateral homogeneously hyperintense adnexal masses. (b) Axial T2WI reveals 'shading' characteristic of endometriotic cysts



**Figure 3:** USG pelvis (4 years post octreotide initiation) shows normal bilateral ovaries with no adnexal mass

**Table 1: Radiological and hormonal parameters while on follow up**

Date	IGF 1 (µg/L)	Growth hormone (µg/L)	Treatment	MRI	Ultrasonography evidence
Basal	955	39.8	Surgery	Uterus normal Rt ovary 3.1×2.8 cm Lt ovary 6.5×6.0	Complex cystic adnexal masses with diffuse low level internal echoes. Left adnexal cyst is larger and multiloculated
At one year	305	1.67	Octreotide started		
At 2 year 1 month	476	2.29	Octreotide continued		Posterior wall uterine fibroid. Bilateral ovarian cysts measuring 22 mm each suggestive of endometriosis
At 2 year 7 months	396	-	Octreotide continued		2.3×2.2 cm Posterior wall uterine fibroid. Bulky ovaries but cysts not seen. Rt ovary 10 cc; Lt ovary 14.4 cc
At 3 years 1 months	136	-	Octreotide continued		
At 3 years 7 months	200	-	Octreotide continued		1.6×1.0 cm posterior uterine wall fibroid. No cysts in the ovaries. Rt ovary 8 cc; Lt ovary 9.2 cc
At 4 years 6 months	172	0.24	Octreotide stopped		Bilaterally normal ovaries

earlier age of onset for familial versus non familial cases points towards a polygenic mode of inheritance of this disease.<sup>[11-14]</sup> Though the exact cause of endometriosis is not known, there are various hypothesis postulated. Some of the proposed hypothesis include-Retrograde menses theory of Sampson, Coelomic metaplasia theory and Mullerian embryonic rest theory.<sup>[5,15]</sup> Dysregulation of a number of genes including aromatase, progesterone receptor and angiogenic factors has been shown in some studies.<sup>[16]</sup> Growth factors have also been implicated in pathogenesis of endometriosis by promoting endometrial proliferation and differentiation.<sup>[17-19]</sup> A key enzyme in estrogen synthesis, aromatase, has also been found to have abundant and abnormal expression in endometriotic lesions.<sup>[20]</sup>

Various kinds of remedies have been tried in the treatment of endometriosis. While managing the disease by hormonal interventions helps alleviate the pain, surgical management is known to address the infertility issues better.<sup>[21-23]</sup> Frequently used medical treatment modalities for endometriosis include combined contraceptive pills, long acting progestins, GnRH agonists and aromatase inhibitors.<sup>[6-8,24,25]</sup> These agents lead to relief by inhibition of ovulation and minimization of menstrual blood flow and volume. These agents bring respite and regression of the lesions in 70-90% patients whereas around 10-30% patients may show recurrence if the therapy is stopped.<sup>[5,10,21]</sup>

The present case along with endometriosis also had the clinical evidence of long standing GH and IGF 1 excess. Reduction in the GH and IGF 1 levels by octreotide therapy caused a gradual improvement in menstrual symptoms and endometriotic lesions. There was a decrease and then a regression of endometriosis as the patient developed hypogonadotrophic hypogonadism. While regression of endometriosis with development of a hypogonadal status is well known, such an improvement in the symptoms or lesions with a decrease in IGF1 levels has not been described earlier.

Growth factors have been implicated in the pathogenesis of endometriosis, however, to the best of our knowledge there has been no reported case of endometriosis and acromegaly occurring concurrently. *In vitro* studies have revealed Insulin like growth factors, TGF-beta, PDGF, beta-FGF and EGF to be potent mitogens for endometrial stromal cells.<sup>[19,26,27]</sup> Annunziata et al.<sup>[28]</sup> studied the effect of JV-1-36, a GHRH antagonist on proliferation and survival of primary ectopic human endometriotic stromal cell (HESC).<sup>[28]</sup> The HESC proliferation was studied by 5-bromo-2-deoxyuridine incorporation and the HESC survival was evaluated by diphenyltetrazolium bromide, cyclic adenosine monophosphate (cAMP) levels, extracellular signal-regulated kinases 1 and 2 (ERK1/2) phosphorylation, and insulin-like growth factor (IGF)-2 mRNA by real-time PCR. The study revealed that JV-1-36, decreased the endometriotic cell proliferation and endurance. It is possible that regression of endometriosis could also be attributed to the decrease in GH and IGF1 levels in the present case.

In conclusion, this was a rare case report where endometriosis and acromegaly coexisted. The treatment of acromegaly concurred with regression in the endometriotic lesions.

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