Hypogonadotropic Hypogonadism with Cushing’s Disease- A Case Report

Deepti Jain1* and Suvrit Jain2
1Department of Gynaecology, Chotu Ram Hospital, Rohtak, Haryana, India
2Senior Resident, Pandit BD Sharma PGIMS, Rohtak, Haryana, India

*Corresponding author: Deepti Jain, Department of Gynaecology, Chotu Ram Hospital, Rohtak, Haryana, India, Tel: 9466594411; E-mail: deeptijain62@gmail.com

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Abstract

A 27 year old woman presented with secondary amenorrhoea. She was obese and had marked pigmentation on face, abdominal striae and severe hypertension. Endocrinal work up revealed low estradiol with low gonadotrophin levels suggesting hypogonadotropic hypogonadism. A magnetic resonance imaging revealed a macroadenoma in the anterior pituitary. A raised cortisol and a raised adrenocorticotropic hormone level confirmed the diagnosis of Cushing’s disease. The pituitary macroadenoma was resected with Leksell Gamma knife radiosurgery. The response on her reproductive function was immediate, as she had spontaneous menstruation just three weeks after surgery. She also became normotensive and is being kept on follow up.

Keywords: Adrenocorticotropic hormone; Cushing’s disease; Hypogonadotropic hypogonadism; Thyroid stimulating hormone

Introduction

Cushing’s disease is a rare endocrinal disorder with little epidemiological data available on the disease. It is estimated to affect 10-15 people per million population each year in United states and is listed in the Office of Rare Diseases of the National Institute of Health (NIH), last updated November 28, 2014 [1].

This girl presenting with amenorrhoea also had conspicuous cushingoid features. An ACTH secreting macroadenoma in the pituitary gland was picked up. A delay in the diagnosis could have led to serious morbidity, in terms of loss of vision as a result of pressure of the adenoma on the optic chiasma. Intracranial haemorrhage and organ failure too could have occurred because of severe hypertension. A hasty surgical resection not only prevented complications but also improved her reproductive function.

Case Report

A 27 year old girl presented on November 25, 2014, in the outpatient clinic with secondary amenorrhoea for the last 4-5 years. According to the patient she was not getting her periods when administered 5 day therapy, probably synthetic progestin. For the last 6 months she was having menstruation with cyclic oral contraceptive pills containing estradiol and norgestrel. She also reported aggravation of acne and increase in facial hair.

On examination, her height was 5 feet 3 inches and she weighed 70 kg; the body mass index was 32, suggestive of obesity. Her blood pressure was 170/110 mm. Acne pustules and pigmentation were seen on the face and facial hair was also increased (Figure 1A) marked hyperpigmentation was visible on the back as well (Figure 1B). The abdomen was broad, flabby with presence of striae and pigmented spots (Figure 1C).
Patient value | Reference Range
--- | ---
Luteinising Hormone | 0.25 miu/ml
Follicle stimulating hormone | 4.40 m iu/ml
Serum Prolactin | 11.49 ng/ml
Tri-iodo thyronine T3 | 0.737 ng/ml
Thyroxine T4 | 6.03 ng/ml
Thyroid stimulating hormone TSH | 0.59m iu/ml
Serum Estradiol | 25.91 pg/ml
Growth hormone | 0.22 ng/ml
Serum Insulin like growth factor-1 | 133.00 ng/ml
Adrenocorticotropic hormone,plasma [ACTH] | 68.20 mg/ml
Total Testosterone | 60.29 ng/dl
Total morning serum Cortisol | 48.67 microg/dl
Serum Cholesterol | 213.2 mg%
Blood Sugar Random | 93 mg%
Serum Creatinine | 1.05 mg%
Blood Urea | 14.52 mg%
Serum glutamic oxaloacetic transaminase | 20.5 iu/l
Serum glutamic pyruvic transaminase | 55.7 iu/l
Serum Bilirubin | 0.604 mg/dl
Dehydroepiandrosterone sulphate | 8.8 ng/ml
Serum Protein total | 7.0 gm/dl
Albumin / Globulin ratio | 1.9

Table 1: Presurgical investigations.

A contrast enhanced magnetic resonance imaging was performed. It revealed that the sella was increased in size and a differentially enhanced lesion measuring 10 × 16 × 8.6 mm was seen in anterior pituitary gland, likely to be a pituitary adenoma (Figures 2A-2C).

The presence of secondary amenorrhoea with low serum estradiol and low luteinising and follicle stimulating hormone levels confirmed the diagnosis of hypogonadotropic hypogonadism. Central hypothyroidism was visible with Thyroxine and Thyroid stimulating hormone on the lower side of the normal range. Somatotroph and lactotroph cells in pituitary gland were however preserved as insulin like growth factor-1 and serum prolactin were normal. A magnetic resonance imaging of pituitary gland suggested a space occupying...
lesion in the anterior pituitary. At the same time typical signs of hypercortisolism i.e. abdominal striae, centripetal obesity and hyperpigmentation were present. Serum cortisol levels were raised suggesting an adrenocorticotropic excess. The presence of an ACTH secreting adenoma in the anterior pituitary gland was further confirmed with a raised laboratory value of ACTH.

The presence of an ACTH secreting adenoma in the anterior pituitary gland was further confirmed with a raised laboratory value of ACTH.

Figure 2B: Sagittal T1W image of pituitary gland showing differentially enhanced Lesion.

Figure 2C: Sagittal T2W image showing bulky pituitary with hyperintense lesion in basal part.

The adenoma was causing pressure on gonadotrophin secreting cells resulting in hypoestrogenism and amenorrhoea. The excess cortisol levels were also causing amenorrhoea because of negative inhibition of the pituitary hypothalamus axis. An earlier ultrasonogram performed on July 7, 2014 reveals a small uterus. However the normal size of uterus seen on November 25, 2014, despite the marked hypoestrogenism was because of the preceding oral contraceptive therapy administered to the patient before coming to us. Serum total testosterone values too were in range owing to oral contraceptives.

Hence the final diagnosis was hypogonadotropic hypogonadism with Cushing’s disease with ACTH secreting pituitary adenoma.

Treatment

She was put on bisoprolol 5.0mg to control hypertension and was urgently shifted to Rancan Gamma Knife centre in New Delhi. Stereotactic dynamic contrast magnetic resonance imaging performed just prior to surgery confirmed the presence of a right sided sellar/ suprasellar pituitary adenoma measuring 911.0 cubic mm. Gamma knife surgery was performed on December 4, 2014. The patient was shifted to gamma knife suite and 99% tumour volume i.e. 901.4 cubic mm was targeted by three shots using three 8 mm collimator shots. Prescription dose equal to or more than 2 0.0 Gy was delivered, 40% prescription isodose configuration with a maximum dose of 50.0 Gy in a single treatment session.

Follow up and outcome

The patient recovered well after the surgical excision. She had her first spontaneous menstruation on December 25, 2014. She became normotensive, her blood pressure was 130/80 mm Hg, three weeks after the surgical procedure. She was investigated on Day 2 of her spontaneous menstruation 2 months after the surgery. Her body mass index improved as her weight was now 66.6 kg. A 14 day follicular study showed a follicle size 16 × 11 mm, implying near normal ovulatory function (Table 2).

<table>
<thead>
<tr>
<th>Patients Value</th>
<th>Normal range</th>
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<tr>
<td>Luteinising hormone</td>
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<tr>
<td>ACTH</td>
<td>98.30 pg/ml</td>
</tr>
</tbody>
</table>

Table 2: Postsurgical investigations done on Feb 13, 2015.

Discussion

This is a unique case with dual presentation of cushingoid features and profound hypoestrogenism. A prevalence of 0.004% has been
reported for Cushing's syndrome in an 18 year study conducted in Spain. The average incidence of newly diagnosed cases was 2.4 cases per million inhabitants per year [2]. Cushing's syndrome is the result of exogenous or endogenous glucocorticoid exposure. Endogenous Cushing's syndrome can be due to ACTH independent or ACTH dependent causes. ACTH dependent or Cushing's disease caused by an ACTH pituitary secreting adenoma is found to occur in about 80-85% cases of Cushing's syndrome [3]. Cushing's disease is associated with unsuppressed or raised ACTH levels despite the hypercortisolism as seen in this woman.

The fatty liver changes on ultrasonogram in this woman could be explained by visceral adiposity and slightly deranged liver functions. She was obese because of the hypercortisolism, as after surgery she lost about 3.4 kg weight in 2 months with no dietary restriction and no change in physical activity.

Two important points intriguing in this case were a normal glycemic status and not very high cholesterol levels. In Cushing's syndrome, due to raised cortisol levels hypercholesteremia and hyperglycemia are very conspicuous.

In a study 6 out of 13 women with Cushing's syndrome i.e. 46% women with moderately elevated cortisol levels ovaries showed morphology similar to polycystic disease. In this woman also the ovaries showed multiple peripherally arranged follicles [4].

Recurrent endometrial hyperplasia not responding to repeat curettage and progestin in a woman was diagnosed to have adrenal cushingoid syndrome. It was due to a 3.1 cm adrenal mass in the left adrenal gland in which hyperplasia was resolved after adrenalectomy [5].

The primary treatment of Cushing's disease is surgical with removal of the corticotroph adenoma by trans-sphenoidal approach and leads to remission of Cushing's disease in 70-90% cases [6].

However in this patient, Gamma knife surgery was used for resection of adenoma. In a recent study Leksell gamma knife radiosurgery was performed on twenty six patients with Cushing's disease and were followed up for 48-216 months. In nine patients gamma knife was used as the primary therapy. Hormonal normalization was seen in 80.7% patients with no recurrence of the disease. Hypopituitarism was not reported in any patient where the crucial dose to pituitary and distal infundibulum was adhered to i.e. not exceed [7]. In another study conducted in 2013 stereotactic radiosurgery was performed in patients with persistent Cushing's disease after prior resection. Tumour control was achieved in 98% patients and new loss of pituitary function occurred in 36% patients [8].

On comparing trans-sphenoidal approach to radiosurgery, presently radiosurgery is a newer noninvasive modality with rapid improvement in pituitary function and very little new loss of pituitary functions as proven in this case.

Medical therapy is the second line therapy employed in acutely unwell patients; or while awaiting response of radiotherapy and rarely in recurrence after surgery. The most often used drugs are Metyrapone and Ketoconazole with serious side effects. Rarely centrally acting drugs or glucocorticoid receptor blockade may be used [9]. Lastly bilateral adrenalectomy may have to be employed in severe Cushing's disease with unresponsive hypercortisolism. Following surgical treatment the patient should be kept on regular follow up with measurement of serum cortisol thyroid stimulating hormone, growth hormone and gonadotrophin levels.

Conclusion

Cushing's disease is a grave disease with a serious risk of mortality. When an ACTH secreting adenoma in the pituitary gland is confirmed it should be urgently treated by gamma knife radiosurgery or surgical excision. The woman should be followed up with periodic endocrinological assays to judge remission and later on recurrence or rarely pituitary failure.

References

1. National Institute of Health office of Rare diseases research, Rare diseases and related terms.