Management of resistant prolactinoma in infertile lady with successful maternal and perinatal outcome

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Received: 24 August 2015
Accepted: 09 September 2015

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ABSTRACT

Mrs. X of 28 years presented to the gynaecology department with primary infertility for 4 years, secondary amenorrhea for 6 months and galactorrhea for 3 months. She was investigated and diagnosed to have macroadenoma. Medical treatment with cabergoline was started. Patient became symptomatically free in 6 months with gradual reduction in serum prolactin levels as well as tumour size. After 2 years of therapy, failure of normalisation of prolactin levels and failure of significant tumour reduction observed and diagnosed it as resistant prolactinoma. Considering her infertility and future complications associated with resistant macroadenoma, she was treated with stereotactic radiosurgery using cyber knife radiation. Tumour regression in MRI with significant decrease in serum prolactin levels were observed in the post radiation period and monthly follow up done. She conceived spontaneously after 2 months of radiotherapy. She has been followed up with visual field testing during antenatal period. Her antenatal, intranatal period was uneventful with successful maternal and perinatal outcome.

Keywords: Resistant prolactinoma, Stereotactic radiotherapy, Cyber knife radiation

INTRODUCTION

Prolactinomas account for approximately 40% of all pituitary adenomas and most commonly presents with secondary amenorrhea and galactorrhea and are an important cause of gonadal dysfunction and infertility. The ultimate goal of therapy for prolactinomas is restoration or achievement of eugonadism through the normalisation of hyperprolactinemia and control of tumor mass. Medical therapy with dopamine agonists is highly effective in the majority of cases and represents the mainstay of therapy. Certain rare conditions of prolactinomas which are resistant to dopamine agonists may require either surgery or radiotherapy or both accordingly.

Ours was a rare and interesting case of primary infertility with pituitary macroadenoma, which initially responded to medical therapy, became resistant after 2 years. In view of resistance to medical therapy and patient being infertile, tumour reduction using stereotactic radiotherapy was performed and it was successful. She conceived spontaneously and delivered a full term child by vaginal route.

CASE REPORT

Mrs. X of 28 years, married for 4 years with previous regular cycles presented with oligomenorrheic cycles for one year, secondary amenorrhea for 6 months and milk discharge from both the breasts for 3 months. Detailed clinical history taken.

Clinical examination

BMI: 26; Vitals – Stable. Systemic Examination: Heart and Lungs – NAD. Breasts – Bilateral milk discharge...
present. Abdominal examination - Soft. Per Speculum and vaginal examination - Cervix and vagina - healthy; uterus - Normal size, mobile, anteverted, fornices were free.

**Investigations**

Base line investigations including USG (abdomen and pelvis): Normal; Endocrinological work up done. Serum FSH, LH, Total testosterone, DHEAS, Thyroid profile-WNL. Serum prolactin levels was found to be abnormally high – 2004 ng/ml. MRI brain revealed a large pituitary tumour measuring 27mm x 22mm x 17mm.

**Diagnosis**

26 years aged infertile lady with pituitary macroadenoma (prolactinoma).

**Management of prolactinoma**

Medical therapy was started with Cabergoline 0.5 mg orally twice a week and gradually increased by 0.5 mg per week with endocrinologist’s advice. Estimation of serum prolactin levels was done monthly. Complete suppression of milk discharge and resumption of menstruation occurred 6 months after initiating the medical therapy. Treatment was continued. MRI brain done after one year for the regression of the tumour size.

**Follow-up**

After one year of treatment, the serum prolactin levels was 530 ng/ml. MRI brain performed for regression of the tumour size and it was found to be 22mm x 18mm x 16mm. Medical treatment was continued. Follow up after second year of treatment showed no considerable tumour shrinkage by MRI (20mm x 17mm x 16mm) and serum prolactin levels was found to be 230 ng/ml. Considering it as resistance to medical therapy, the diagnosis of resistant prolactinoma was made.

**Management of resistant prolactinoma**

In view of infertility and considering her future complications associated with the resistant tumour, further treatment option was planned. Success rates, complications, patient’s affordability with regard to the surgical and or radiotherapy procedure was analysed and preceded with stereotactic radiotherapy using cyber knife radiation with 25 Gy in 5 fractions for 5 days daily on an op basis. Post radiation MRI brain showed tumour resolution.

**Post radiation follow-up**

Serum prolactin levels were used as a monitoring tool and monthly estimation was done. Gradual decline in the serum prolactin levels were observed. She was started on Bromocriptine 2.5 mg once daily. She conceived spontaneously in the second follow up visit.

**Post conception follow-up**

Antenatal investigations and dating scan done. Routine antenatal care given. Bromocriptine was continued till the end of the first trimester. Apart from this, visual field charting was performed during each trimester for any regrowth of the tumour and visual fields were found normal. IFA prophylaxis, Inj.TT two doses, anomaly scan, regular antenatal check-ups, laboratory investigations and fetal growth scans were performed. Her antenatal period was uneventful. She went into spontaneous labour at 39 wks. of gestation and delivered an alive male child of weight 2.8 kgs. with good apgar by normal vaginal delivery.

**DISCUSSION**

Prolactinomas are the most common type of functioning pituitary tumours, accounting for approximately 50-60% of functioning pituitary adenomas and represent 30-40% of all pituitary tumours. It is seen most commonly among reproductive age group and is an important cause of hypogonadism and infertility. Macroprolactinomas with more than 10 mm in diameter have high serum prolactin concentrations exceeding 200 µg/lit with or without symptoms related to tumour expansion such as headache, visual disturbances and cranial nerve dysfunction. The treatment goal is aimed at maintaining eugonadism by reduction of serum prolactin concentrations and tumor mass to prevent pressure symptoms related to tumour expansion and prevention of disease recurrence.

Medical therapy with dopamine receptor agonists is the initial treatment of choice. Cabergoline is more effective than bromocriptine and is considered as first-line agent as it has higher affinity for dopamine receptor binding sites with superior drug compliance and low incidence of side effects.

In our case, Cabergoline was started initially with 0.5 mg twice weekly and it was increased step wise to 3 mg per week. As there was no considerable response, the dose has been increased further up to 7 mg per week. Ono M et al in 2008 conducted a prospective study of high dose cabergoline for the treatment of prolactinomas in 150 patients and found that individualised high-dose cabergoline treatment can normalize hyperprolactinemia in nearly all prolactinomas irrespective of tumor size or preceding treatments. Our case was followed up by estimating serum prolactin levels monthly and MRI brain yearly for reduction of the tumour size. The patient initially responded to medical treatment but after 2 years there was no considerable decrease in serum prolactin levels as well as tumour shrinkage with failure in the restoration of fertility.

Failure to achieve normal prolactin levels with maximum tolerated doses of dopamine agonist, failure to achieve a 50% reduction in tumor size and failure to restore fertility
with standard doses of dopamine agonists are considered as resistant prolactinomas.9

The treatment options available for this case were surgery and or radiotherapy. Even though surgical approach is considered as the gold standard treatment, for macroadenomas the tumour resection would be difficult as it lies adjacent to critical neurovascular structures. The success rates are highly variable ranging from 6.7 to 80% and recurrence rate being 7-50%.1011 Maiter D et al in 2014 reviewed the management of giant prolactinoma cases and found that the extensive tumours are usually not completely resectable and neurosurgery has significant morbidity and mortality.12 So additional therapy after operation using conventional external radiation may be needed, but it takes several years to achieve endocrinalological remission and risk for panhypopituitarism or visual disturbances exists.

In the recent years, stereotactic radiosurgery evolved as an important treatment modality alternative to surgery and conventional radiotherapy. It uses high doses of focused radiation beams targeting for the tumour destruction thus achieving growth control and hormonal remission with minimum neurological complications and radiation injury to surrounding structures with a documented efficacy of 76-95%. It is a non-invasive procedure with fewer complications. Kajiwara K et al in 2010 reviewed the clinical results of stereotactic radiosurgery and found that the image-guided stereotactic radiosurgery is effective and safe against pituitary adenomas,13 this patient was given stereotactic Cyber knife radiation using 25 Gy in 5 fractions for 5 days. Post radiation MRI showed tumour regression and considerable decrease in serum prolactin levels was observed. She was started on bromocriptine 2.5 mg once daily and followed up.

The patient conceived spontaneously after 2 months of treatment. Routine antenatal check-ups, investigations and ultrasound were done and found normal. In those patients who underwent debulking pituitary surgery or pituitary irradiation before pregnancy, the risk of symptomatic growth was found to be 2.8%.14 Almalki MH et al in 2015 found that the risk of tumor enlargement in pregnancy may occur in 4.8% of those with macroadenomas with prior ablative treatment.15 In view of the likely chance of tumour recurrence during pregnancy, formal visual field testing in each trimester was performed. Measurement of serum prolactin levels are not recommended as physiological increase in serum prolactin levels during pregnancy do not accurately reflect the changes in tumour growth or activity. MRI without gadolinium is advices in the presence of pressure symptoms like headache or visual field changes and medical treatment with bromocriptine is recommended. If the symptoms persist, surgical debulking is advised.

In our case the antenatal period was uneventful. Mode of delivery is like any other obstetric case. Our case went into spontaneous labour at 39 weeks of gestation and delivered vaginally an alive female child of weight 3.1 kgs with good appgar. In the post-partum period, contraceptive advice is given according to the patient’s choice. Postnatal period was uneventful in our case. Contraceptive advice given and follow up done.

CONCLUSION

Prolactinomas are one of the rare and important causes of infertility in females. Dopamine agonists are considered as the first line of treatment. For medically resistant cases, in the recent years, stereotactic radiosurgery is found to be effective in tumour regression and normalisation of serum prolactin levels with fewer complications. The chances of fertility are found high in the post radiation period. During pregnancy, monitoring is done by visual field charting in each trimester for regrowth of the tumour apart from the routine antenatal care. Measuring serum prolactin levels is not recommended in pregnancy. There is no contraindication for vaginal delivery. Contraceptive advice is given according to the patient’s choice.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES


