

**Case Report**

Giant Macroadenoma with an Unusual Extension: A Case Report and Literature Review

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Abstract: Giant prolactinomas are rare tumors, representing only 2-3% of all prolactin (PRL)-secreting tumors. The management of giant prolactinomas remains a major challenge. Here we report the case of a young man aged 31 years old, followed up for a giant and invasive pituitary macroadenoma of 5cm discovered during a neuro-ophthalmic syndrome. The initial hormonal exploration and follow-up evaluation concluded hyperprolactinemia at 138.5ng/mL, anterior pituitary insufficiency and bilateral blindness related to optic atrophy. Incomplete surgical resection was performed after one month of medical treatment with a dopaminergic agonist. Histologic examination showed an aspect of an invasive macro-adenoma with no signs of malignancy. Despite therapeutic escalation, the evolution was marked by the persistence of resistant hyperprolactinemia. A control MRI was done showing a voluminous extra-axial expansive process measuring 9cm with significant anterolateral and inferior extension in the cavum and nasal fossae. A biopsy of the tumour in the nasal fossae was done showing morphological aspects and an immuno-histochemical profile of an aggressive lactotropic adenoma of the type "Acidophilic stem Cell adenoma" with an over expression of p53. External radiotherapy was indicated, but the patient died rapidly in a brain engagement table. This case illustrates the difficulty in the management and control of invasive and aggressive pituitary adenomas and their unpredictable course.

Keywords: Giant Prolactinoma, Pituitary Tumor, Cabergoline

1. Introduction

Prolactinomas are benign tumors of the pituitary gland, accounting for 30–40% of all pituitary adenomas, commonly present as small intra-sellar microadenomas in women, but may be much larger in men, presenting as macroadenomas of more than 1 cm in diameter. Giant prolactinoma is a rare tumor, defined as tumors >4 cm, with very high plasma prolactin levels usually >1000 ng/mL and with clinical symptoms of hyperprolactinemia or mass effect [1]. Giant prolactinomas comprise only 2% of all pituitary tumors in large series [2, 3] and much more prevalent in young to middle-aged men, with a

male to female ratio of about 9:1 and a mean age around 40 years [2–6]. Endocrine symptoms are often present but overlooked for a long period of time, and diagnosis is made when neurologic complications arise from massive extension into the surrounding structures. Currently, the management of giant prolactinomas is still a major challenge. Dopamine agonists are the first line treatment, as they effectively normalize PRL levels and reduce tumor volume [7]. Surgery is indicated for intolerant or resistant cases.

The purpose of this paper is to describe clinical, radiological features, the treatment modalities and outcomes of this case of giant prolactinoma and review of the literature.

2. Case Presentation

A 31 year – old married man and father of three children was followed up for a giant invasive pituitary macroadenoma of 5cm discovered during a neuro-ophthalmic syndrome. Laboratory evaluations showed hyperprolactinemia at 138.5 ng/mL and further evaluations revealed central hypogonadism, secondary hypothyroidism, adrenal insufficiency and normal IGF1 level (Table 1). The patient suffered also from bilateral blindness related to optic atrophy and complete right ptosis (Figure 1). Incomplete surgical resection was performed after one month of medical treatment with cabergoline (a dopamine agonist), levothyroxin and hydrocortisone. Histologic examination showed an aspect of an invasive macroadenoma with no signs of malignancy. The immuno-histochemical study was unfortunately not done. Control prolactinemia was

238 ng/ml. Despite therapeutic escalation, the evolution was marked by the persistence of resistant hyperprolactinemia. The clinical course was marked by an alteration in general condition with minimal bilateral epistaxis. A control MRI (Figure 2) was done showing a voluminous extra-axial expansive process measuring 9cm with significant anterolateral and inferior extension in the cavum and nasal cavity.

Then, the patient was referred to our department of endocrinology. A biopsy of the tumour in the nasal fossa was done showing morphological aspects and an immuno-histochemical profile of an aggressive lactotropic adenoma of the type "Acidophilic stem Cell adenoma" with an over-expression of p53 (Figure 3). External radiotherapy was indicated, but the patient died rapidly from brain involvement.

Table 1. Hormonal evaluation.

| Hormone | Normal range | Initial workup | 1 month postoperative | 3months postoperative | 9monthspostoperative |
|----------------------------|---------------|----------------|-----------------------|-----------------------|----------------------|
| Prolactin (ng/ml) | <25 | 138.5 | 237.8 | 341 | 461 |
| FSH (mUI/ml) | 1.5-7 | 2.29 | ---- | ---- | 1.06 |
| LH (mUI/ml) | 1.1-11.7 | 0.99 | ---- | ---- | 0.3 |
| Total testosterone (ng/ml) | 2.8-8 | 0.4 | ---- | ---- | 0.3 |
| Cortisol (ng/ml) | 80-180 | 63 | ---- | ---- | 80 |
| ACTH (pg/ml) | 10-55 | 12 | ---- | ---- | ---- |
| FT4 (pmol/l) | 12-22 | 9.03 | ---- | ---- | 10.1 |
| TSH (mUI/l) | 0.27-4.2 | 1.98 | ---- | ---- | ---- |
| IGF1 (ug/l) | Age-dependent | 118 | ---- | ---- | 114 |
| GH (ng/ml) | 0.11-2.47 | 0.04 | ---- | ---- | 0.04 |

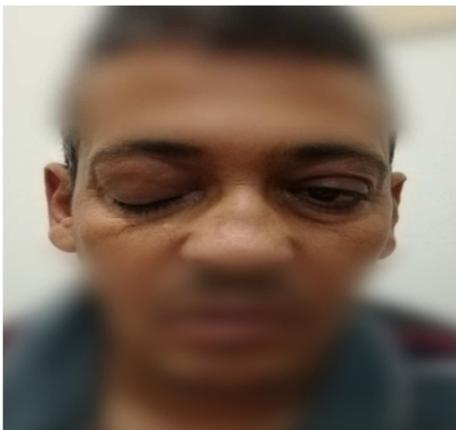


Figure 1. Complete right ptosis.

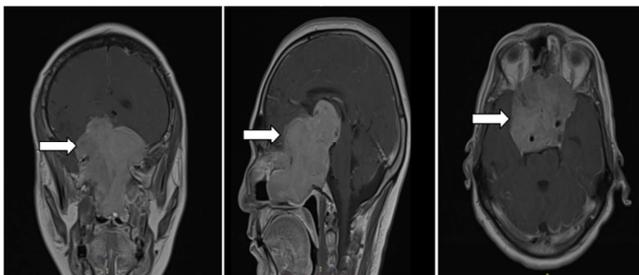


Figure 2. Axial, coronal and sagittal T1 MRI cross-sections of pituitary macroadenoma (white arrow).

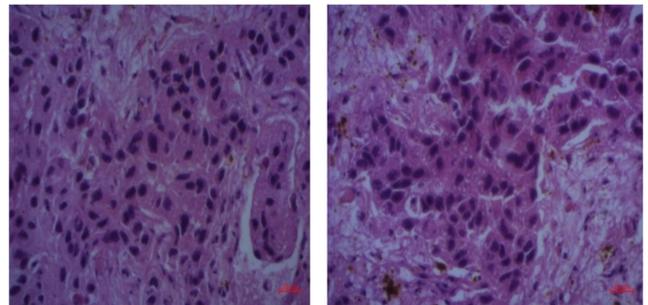


Figure 3. Histological sections of the tumour.

3. Discussion

A giant macrolactinoma is defined as any adenoma greater than 4cm in size and is generally associated with a prolactin level >1000ng/m [8, 9]. Giant prolactinomas are very rare, representing only 2-3% of all PRL-secreting tumors [2, 7]. Typical symptoms of hyperprolactinaemia or pituitary mass are observed in a significant subset of patients but overlooked for a long period of time. A review of available literature shows that primary or secondary amenorrhoea is reported in more than three-fourths of women with a giant prolactinoma, male hypogonadism in 61%, visual problems and recurrent headaches in 71 and 59% of patients respectively. Data regarding galactorrhoea are often missing and the observed rate of 10% might be underestimated. This feature is rare in men and

it is reported in a recent study in 8 of 24 women with a giant prolactinoma (33%), all younger than 50 years. The presence of hypopituitarism is observed in about one third of patients in whom information is available [10]. Typical presentations are quite frequent and usually reflecting a large tumor extension into the surrounding intracranial structures. Giant prolactinomas frequently invade the sphenoid, ethmoid and/or cavernous sinus or the clivus. Giant prolactinomas may extend laterally in the cavernous sinus and frequently cause cranial nerve palsies [11]. Orbital invasion is another rare extrasellar extension of pituitary tumors and will cause exophthalmos and optic nerve compression at the orbital apex [12]. Finally, invasion of the nasopharynx has also been described and will produce nasal stuffiness, snoring and epistaxis, and the diagnosis of prolactinoma may sometimes be made through biopsy of a nasal polypoid mass [13, 14]. That was the case with our patient. Giant prolactinomas are usually accompanied by a high serum prolactin concentration; extremely higher up to 50,000–80,000 ng/ml is rare [15]. Lower PRL concentrations (between 250 and 1000 mg/l) may be rarely observed in giant prolactinomas. However, such discordance between tumour size and hormonal levels should always prompt a new measurement of PRL concentrations after serial dilution to remove the hook effect and, if confirmed, will usually result from a large necrotic or hemorrhagic component or from a heterogeneous histopathological content [10]. Those assumptions don't explain our patient's case. According to the literature, our patient's histological type "Acidophilic stem Cell adenoma" is characterized by low hormonal activity, which explains the low prolactin level [16]. It is also characterized by resistance to medical treatment explaining the lack of normalization of prolactin levels despite the escalation in treatment. The aggressiveness of this tumor was explained by an overexpression of P53.

Complete surgical removal of giant tumor is difficult and biochemical cure is rare [17–19]. In prolactin – secreting macroadenomas, goals of treatment are to decrease tumor size, improve visual field defects and restore sexual function. Dopamine agonists are able to reach these goals with reducing tumor size [20, 21].

In comparison with bromocriptine, cabergoline has fewer side effects and more positive effects at normalizing prolactin levels [22, 23]. If visual field defect persists and chiasmal compression on MRI examination continues despite optimal medical treatment, surgery will be inevitable. But little is known about the role of dopamine agonist therapy in treatment of giant invasive prolactinomas. There were studies evaluating cabergoline (a dopamine agonist) in management of giant prolactinoma [7, 21, 24]. All of these studies showed that cabergoline is safe and well-tolerated and also suggested that cabergoline should be the first line of treatment for giant aggressive macroprolactinomas.

Finally, medical therapy needs to be maintained almost invariably lifelong in the setting of a giant prolactinoma, even in case of very favorable response. The morbidity and mortality rates associated with surgical intervention are considerably higher for giant pituitary adenomas than for

smaller, non-invasive adenomas [25]. So surgery should be restricted to some acute complications or to resistant patients in which a significant debulking is feasible. Radiotherapy may be used post-operatively in aggressive and proliferative giant tumors, which are not controlled by Dopamine agonist's treatment [26], although there is no prospective study demonstrating its usefulness in this setting. Adjuvant radiotherapy should be considered in the setting of a clinically relevant invasive tumour remnant with pathological markers (Ki67 index, mitotic count, p53 immunodetection) strongly indicating aggressive behavior [27].

4. Conclusion

Giant prolactinoma are rare tumors with male preponderance. Positive diagnosis of invasive adenomas has become easier with recent morphological and histological approaches, but their therapeutic management remains complex. This case illustrates the difficulty in the management and control of invasive and aggressive pituitary adenomas and their unpredictable course.

Consent

Written informed consent was obtained from the patient and it is available for review.

Conflicts of Interest

The authors declare that they have no competing interests.

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