Brief Communication

Resistant prolactinoma: Is it monoclonal or polyclonal?

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ABSTRACT

Prolactinomas are solitary benign neoplasms and resistance to dopamine agonists occur in a small percentage of prolactinomas. Multiple pituitary adenomas are reported in less than 1% of pituitary adenomas and rarely result in resistant prolactinoma. We recently encountered an interesting patient of hyperprolactinemia with multiple pituitary microadenomas. Dopamine agonist use resulted in prolactin normalization and subsequent pregnancy resulted in drug withdrawal. Repeat evaluation after delivery showed a macroprolactinoma and dopamine agonist therapy resulted in biochemical cure without reduction in tumor size. We report the case for its presentation with multiple microadenomas progressing to macroprolactinoma suggesting polyclonal in origin.

Key words: Multiple pituitary adenoma, polyclonal, resistant prolactinoma

Introduction

Prolactinomas are benign neoplasms representing clonal proliferation of pituitary cells. They are very sensitive to dopamine agonist therapy and biochemical resolution is usually associated with a reduction in size of the tumor. Resistant prolactinoma is defined as the failure to achieve biochemical control and/or reduction in tumor mass with dopamine agonist therapy.[1] Resistance is usually associated with aggressive prolactinomas, altered dopamine receptor expression, malignant transformation of the tumor, and double pituitary adenoma. Multiple pituitary adenomas are described in approximately 1% of pituitary autopsy series. The majority of reports suggest double adenomas with distinct histological features and immunophenotypes.[2] Growth hormone producing adenoma is commonly associated in combination with others in double or multiple pituitary adenomas.

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Pituitary tumors arise as clonal expansions of genomically altered cell. Adenomas may be multicentric in appearance or through different clonal proliferation within the original adenoma resulting in diverse phenotypic expressions.[3] The etiopathogenesis of prolactinoma is unclear as regards hypothalamic dysregulation leading to lactotroph hyperplasia or due to a single mutation leading to monoclonal origin.[4] We report the natural history of a macroprolactinoma in a patient who initially presented with multiple microadenomas. We report the case for its unusual presentation and highlight the pathogenetic basis behind the origin of prolactinomas.

Case Report

In January 2012, a 32-year-old lady was referred to our department for evaluation of a resistant prolactinoma. She presented to a peripheral hospital initially in February 2010 with a history of galactorrhoea and menstrual irregularity of 6 months duration. She complained of occasional episodic headache, not associated with vomiting, seizures, altered sensorium, and visual field defects. There was no history to suggest thyroid dysfunction, systemic or psychiatric ailment, and drug intake. She denied features to suggest a disturbance of any other hormonal axes or similar history in family members. Her initial evaluation revealed normal vital parameters with no evidence of

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goiter. Systemic examination was normal except for galactorrhoea. Her neurological examination was normal including visual fields and fundus examination. Hormonal profile revealed hyperprolactinemia (serum prolactin 289 ng/ml) with normal thyroid, adrenal, gonadal, and growth axes evaluation. Magnetic resonance imaging (MRI) sella revealed multiple, small, focal, well-defined, abnormal areas of signal intensity in the anterior pituitary on both sides [Figure 1]. Lesions appear homogeneously hypointense on T2 weighted images with minimal enhancement after contrast. Dynamic mean curve analysis shows slow uptake of contrast with low peak by the lesions suggesting a diagnosis of multiple pituitary microadenomas. There was no pressure effect on surrounding structures. The patient was treated with cabergoline 0.5 mg biweekly and continued for another 6 months. She had regular menstrual cycles and galactorrhoea subsided after 2 months of therapy.

In July 2010, the patient had conceived leading to withdrawal of cabergoline therapy. The patient did not have any features of raised intracranial tension throughout pregnancy and neuroimaging was not repeated for monitoring. She had an uneventful pregnancy and delivered a healthy baby at term. Nine months after delivery she presented with headache and occasional vomiting. Serum prolactin was elevated (158 ng/ml) and the patient underwent repeat neuroimaging. On dynamic and contrast enhanced MRI, pituitary gland appears heterogeneously bulky macroadenoma of 12 × 14 × 15 mm predominantly involving the right half of the anterior pituitary [Figure 2]. The lesion had a mixed pattern of contrast uptake and had no pressure effects on the surrounding tissue. The repeat hormonal panel revealed the normal function of anterior and posterior pituitary. Visual field examination by perimetry was normal and other hematological/biochemical parameters were normal including lipid profile. She was diagnosed to be a case of macroprolactinoma and was treated with cabergoline 0.5 mg weekly. The prolactin level normalized after 3 months with no recurrence of galactorrhea. However, repeat neuroimaging after 6 months did not show any resolution in the size of the pituitary macroadenoma. She continued to receive cabergoline and had no clinical features of hyperprolactinemia or pressure symptoms.

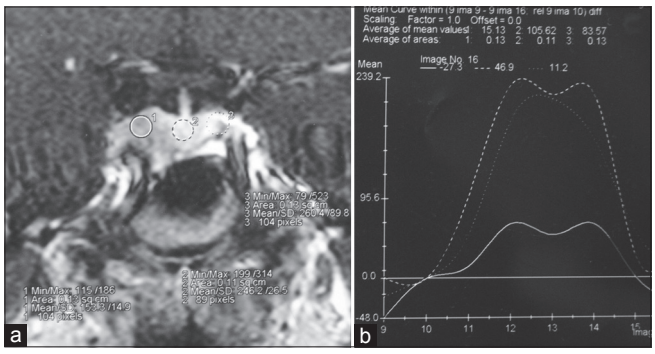

Figure 1: MRI showing (a) multiple microadenomas and (b) with dynamic mean curve analysis

Discussion

To the best of our knowledge this is the first case reported in English literature of multiple microadenomas progressing to a macroprolactinoma. Our patient had typical features of prolactin excess initially and pituitary imaging revealed multiple microadenomas. Dopamine agonist therapy normalized the prolactin, and a subsequent drug holiday during pregnancy led to uniform growth of these microadenomas resulting in a macroprolactinoma. The temporal profile and available imaging findings suggest conversion of microprolactinomas to macroprolactinoma in our patient, though adenomectomy was not done for lack of indications.

The pathogenesis of pituitary tumors is complex with suggestion of genetic aberrations or a hormonal dysregulation due to hypothalamic factors.[2] Genetic mutations are not reported commonly in sporadic pituitary tumors other than those associated with multiple endocrine neoplasia. If prolactinomas arise due to hypothalamic dysregulation, presumably there would be diffuse lactotroph hyperplasia, followed by tumor formation. Molecular analysis may provide information regarding multidirectional phenotypic differentiation. Previous reports could not demonstrate a structural genetic abnormality (rearrangement, deletion, or mutation) in pituitary tumors which could result in transcriptional activation in these tumors.[5] There is strong evidence to suggest that sporadic mutation as the primary etiology against the hypothalamic stimulation. Our patient also supports the same by having multiple microadenomas initially with prolactin excess and later on culminating into the formation of a macroprolactinoma.

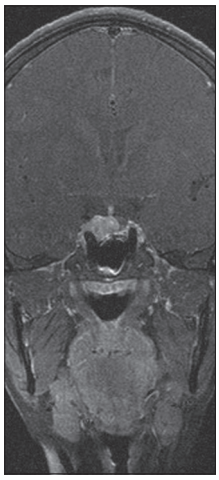

Figure 2: MRI showing pituitary macroadenoma

The occurrence of double pituitary adenoma represents concurrent development of two independent tumors or transformation of one tumor into another type. Pituitary adenomas with multiple histological types have rarely been described.[6,7] Previous report suggests the coexistence of prolactinoma with a gonadotroph adenoma resulted in resistance to the medical therapy.[8] The limitation of our report is the lack of histopathology and molecular analysis of the adenoma. However, the same was not possible as the patient had no indication for adenomectomy.

Conclusion

To conclude, we report the presentation of multiple microadenomas progressing to macroprolactinoma supporting the pathogenesis of a polyclonal origin of the prolactinomas.

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