Mucinoid breast cancer with neuro-endocrine phenotype in a patient with prolactinoma. Is there a link?

Abstract

The association of hyperprolactinemia and breast cancer remains a controversial with respect to pathogenesis of breast malignant tumors in humans. We present the case of a 40-year-old woman with prolactinoma who subsequently developed mucinous breast cancer with neuroendocrine differentiation. While serum prolactin was controlled by dopamine agonists for longer than 4 years at the time of breast tumor diagnosis, positive immunostaining for prolactin in the tumor cells supports an autocrine/ paracrine role of prolactin in breast proliferation. A review of literature on prolactin involvement in breast carcinoma is supporting this hypothesis.

Keywords: *prolactin, breast cancer, mucinoid, neuro-endocrine, prolactinoma*

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Introduction

The role of prolactin (PRL) in the pathogenesis of breast cancer has been debated for decades and is well documented in rodents. However, there are only few cases to support it in humans. While clinical trials with dopamine agonists have failed to improve breast cancer outcome, there is evidence for a significant association of PRL plasma level and subsequent breast cancer risk in postmenopausal women[1]. Case control studies had inconsistent results, therefore autocrine and paracrine actions of PRL within mammary tissue are just speculative. *In vitro* studies showed that breast cancer cells express various PRL receptor isoforms differently than normal breast cells and also synthesize more PRL than the normal cells[2].

In support of the role of PRL in breast cancer pathogenesis, we present the case of a 47-year-old woman with a 6-year history of prolactinoma who subsequently was diagnosed with breast cancer.

Case presentation

A 40-year-old woman, first presented in February 2002 with a 3-month history of hypomenorrhea and intense headaches. She had no galactorrhea and her menses were quite regular, though she associated primary infertility. She had no family history of breast cancer. Initial hormonal assessment revealed markedly elevated levels of PRL (>1000 ng/mL) (normal <20ng/mL), normal random GH (0.39 ng/mL), morning plasma cortisol (12.68µg/dl) and thyroid function tests (Table 1).

The pituitary computed tomography (CT) scan revealed a polycyclic macroadenoma of 4/4.45/4.25 cm (Figure 1a), with suprasellar extension and invasion into the left cavernous sinus and left temporal lobe. The visual field exam showed an amputation of the temporal area of 15 grades on the right eye.

High dose therapy with dopamine agonist (bromocriptine 30 mg/day) was started. Three months later, prolactin decreased to 52.29 ng/mL, but the menses stopped one more month after, when pregnancy was confirmed. Due to invasive macroprolactinoma, estrogen stimulus associated with pregnancy was considered to be dangerous, and the patient was counseled towards termination of pregnancy.

Six months later, the CT scan of pituitary confirmed an important shrinkage of the tumor to 2.1 by 1.2 cm, with a prolactin level of 30.13ng/mL (Table 1). During the following 3 years, bromocriptine was progressively reduced to 15 mg/day, while the visual field normalized, the pituitary adenoma further decreased to 1.3 by 0.9 cm (Figure 1b), and the prolactin level dropped to 4.02 ng/mL. The patient had also received thyroid hormone replacement for sporadic hypothyroid micronodular goiter. Low dose bromocriptine (7.5 mg/day) was continued for another 4 years (2007-2011) while the tumor continued to shrink (Figure 1c).

In December 2005, at the age of 44, the patient's first mammogram was consistent with fibrocystic changes (Figure 2). Subsequent breast ultrasound did not reveal any focal lesions. One year later, at the age of 45, the breast exam revealed a lump in the upper-outer quadrant of the left breast associated with orange peel skin changes. The ultrasound confirmed a 1.5 cm nodule and the biopsy revealed a mammary carcinoma.

Total mastectomy and axillary lymph nodes excision were subsequently performed, and the pathology report showed a T2G1N0, mucinous carcinoma.

The tumor was pink-translucid, 2.8 by 2 cm in size, with no capsule, and with carcinomatous infiltration in the surrounding mammary gland and in the pectoralis major fascia. The resected tissue was positive on immunohistochemistry for estrogen and progesteron receptors and also for prolactin (Figure 3). Human

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Table 1 Hormonal and imagistic follow-up of pituitary tumor

Year/ Treatment	Feb. 2002 (Pretreat.)	Apr. 2002 Brc=30mg/d	Nov. 2002 Brc=30 mg/d	Jan. 2005 Brc=15 mg/d	Jan. 2007 Brc=7.5mg/d	Jun. 2009 Brc=7.5mg/d	Apr. 2011 Brc=7.5mg/d
Hormone profile	PRL>1000 ng/mL random GH 0.39 ng/mL	PRL 52.29 ng/mL Cortisol 10.38 µg/dL	PRL 30.13 ng/mL Cortisol 7.48 µg/dL	PRL 4.2 ng/mL	PRL 5.41 ng/mL	PRL 2.14 ng/mL	PRL 1.58 FSH 30.07 LH 12.68 mUI/mL
Pituitary CT scan Adenoma	4 /4.45/ 4.25 cm		2.1 /1.2 cm	1.5/0.72cm	0.87/0.71cm	1.14/0.7 cm	1.1/1.0 mm

Brc=Bromocriptine

epidermal growth factor receptor (EGFR) type 2 expression was rarely present in vessels on immunostaining and CerB2 was negative. Ki-67 staining revealed that 5% of the tumor cells were positive.

Local radiotherapy and hysterectomy and bilateral salpingo-ophorectomy were subsequently performed.

Five years later at follow-up (April 2011), the patient was on tamoxiphene and on bromocriptin 7.5 mg/day, with no signs of tumor recurrence, with follicle stimulating hormone of 30 mUI/ml, low PRL (1.58 ng/ml), while the pituitary adenoma of 1 by 1.1 cm appeared with near complete necrosis on CT scan. The patient was also vitamin D deficient (25 OH vit D 9.11 ng/mL) normocalcemic with secondary hyperparathyroidism (83.17 pg/mL) and euthyroid on thyroid replacement therapy.

Discussion

Mucinous breast carcinoma accounts for 0,5-3% of breast cancers. Usually, it is associated with a better prognosis than infiltrating ductal carcinoma and a low rate of recurrence[3]. This tumor type is more frequent in older patients and has a lower incidence of local lymph nodes metastasis which is the most important prognostic factor.

There are two major types of mucinous carcinomas: type A (pure - 90% - mucinous carcinomas with no neuroendocrine differentiation) and type B (hypercellular or with neuroendocrine differentiation). The intermediate form AB has 75-90% coloid component[4].

We considered the reported case to be an intermediate form type AB of mucinous carcinoma. It had a predominent mucinous part (Figure 3a) with a Ki67 of 5% and patches with dense cellularity (Figure 3b) that expressed PRL on immunohistochemical staining (Figure 3 c), which pleads for neuroendocrine differentiation. Dedifferentiation of mucinoid breast cancer into neuroendocrine phenotype is rare in young women, but quite often in older patients[4,5].

The mucinous histological type of our patient breast tumor explains the latence in diagnosis as up to 87% of these tumors are palpable at diagnosis[6]. Most of these cancers are isoechoic on ultrasound and 17% are mammographically occult. Some microcalcifications can be seen, but less frequent than in other tumor types. On magnetic resonance imaging (MRI) they gradually enhanced the contrast substance and they have a very intense signal on T2 images. The neuroendocrine tumors had no specific imaging presentation[3].

Only few epidemiologic studies have examined the relationship between PRL and mammary carcinomas. Family

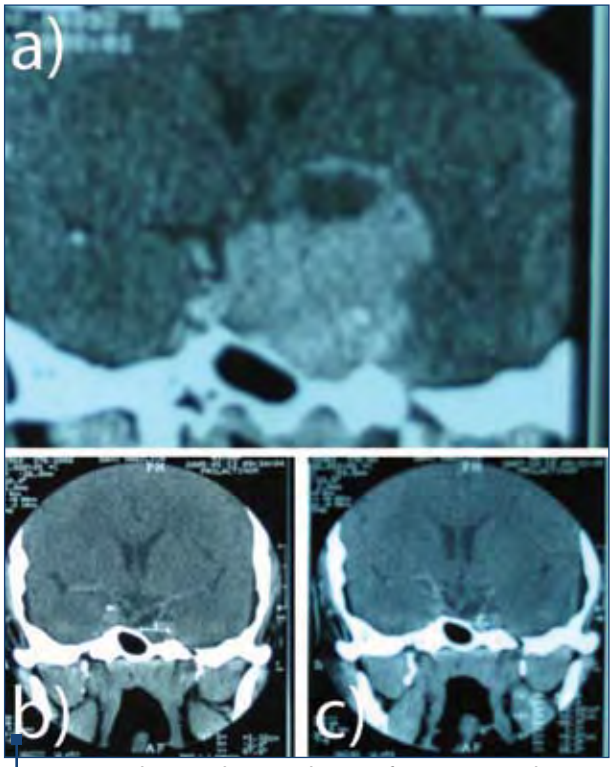

Figure 1. Serial computed tomography scans of pituitary macroadenoma (a) at diagnosis, (b) at 3 years (b) and (c) at 5 years follow-up. Shrinkage of the tumor is observed during bromocriptine therapy

history of breast cancer, or increased mammographic breast density seem to be associated with high PRL level. There is not enough evidence to support association of risk factors such as age at menarche, at first birth or at menopause with high PRL levels[7,8].

Epidemiologic data for premenopausal women are sparse. One study with 235 cases reported a significant positive association between plasma prolactin levels and breast cancer risk. Studies in postmenopausal women have reported a positive association as well. Overall, the available data support the hypothesis that prolactin may increase the risk of breast cancer[9]. Experimental data indicate that prolactin can promote cell proliferation and survival, increase cell motility, and tumor vascularization[10-14].

Sato et al. in 2007 have reviewed only 9 cases of mammary carcinomas that also associated hyperprolactinemia that have been reported. Four of the patients were male. In all 9 cases

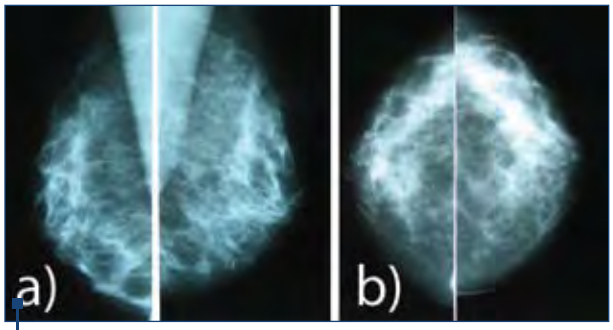

Figure 2 a and b. Mamogramm with fibrocystic changes, but no focal lesion revealed one year before breast cancer diagnosis, at 3 years of prolactinoma follow-up

Figure 3. Breast tumor histology. (a) HE staining, mucinous component; (b) HE staining of tumor neuroendocrine component 4x magnification; (c) immunohistochemistry positive for prolactin 20x magnification

there was positive expression for hormone receptors. In the majority of the cases reported, the pituitary adenomas preceded the diagnostic of breast cancer which raised even more the possibility of the involvement of PRL in its etiology[15].

A population-based matched cohort study in Sweden studied the association of hyperprolactinemia in 384 patients and overall risk of cancer and found a small increase in overall cancer risk in hyperprolactinemia patients, but this was not due to an increased number of breast or prostate cancers, but to upper hematopoietic cancers[16,17]. Although the number of breast cancer cases in their study was low, this is in agreement with the study by Dekkers and contributors[18] who found that the relative risk of breast cancer in 1342 patients with treated hyperprolactinemia was 1.07 (95% CI: 0.50-2.03).

Herranz and colleagues have recently published the results of a 253 cohort of women with invasive breast carcinomas that revealed the presence of hyperprolactinemia at diagnosis of ductal carcinomas only in 6% of the cases. These were also associated with increased age and intense Bcl-2 expression in the breast tumor tissue, but no other prognostic factors[19].

Clevenger and Vonderhaar proved that culture cells from breast tumors can synthesize quite important quantities of PRL[20]. The initial report by Reynolds and contributors using in situ hybridizations later confirmed by orther studies, has proved that PRL receptors are expressed in almost 98% of all human mammary carcinomas[21-23].

In our case the hyperprolactinemia from prolactinoma preceding the breast cancer detection by at least 4 years, may have had a role on breast cancer pathogenesis, considering dormant malignant cells may exist in subclinical cancers more than 5 years before diagnosis. However the sustained control of prolactinemia in this patient supports more an autocrine/paracrine action of locally produced PRL in stimulating the proliferation, growth and motility, of the human mammary tumor cells. We consider less likely that dopamine agonist treatment would have had an influence over the cancer risk in this patient, as a recent meta-analysis evaluating cancer risk in patients with Parkinson's disease, often treated with high doses of dopamine agonists, showed significantly reduced cancer risk ratios[24].

Conclusions

We presented one case of association between prolactinoma and breast cancer with neuroendocrine differentiation, in which hyperprolactinemia may have a pathogenic role in the development of breast tumor.

The mucinous breast cancer in our patient may have progressed more rapidly either due to the locally produced prolactin, or in a context of pituitary induced hyperprolactinemia.

Further prospective studies need to better define this relationship, as well as the possible role of genetic markers in determining the variability of prolactin actions in breast cancer. ■

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