CASE REPORT

Pituitary prolactin-secreting macroadenoma combined with bilateral breast cancer in a 45-year-old male

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ABSTRACT. We describe an unusual case of bilateral breast cancer synchronous with pituitary macroprolactinoma in a young male. Up to date, only very few of such cases have been described worldwide and to our knowledge this is the first one in which both breast cancer and pituitary macroadenoma have been found together at the time of presentation. A 45-year-old male was diagnosed as having a pituitary macroprolactinoma and bilateral breast cancer on the basis of hypogonadism (testosterone 2.9 pmol/l) with very high levels of prolactin (33,100 U/l), typical neuroradiologic finding of a pituitary macroadenoma, marked bilateral gynecomastia with mammographic pattern highly suspected for cancer and subsequent hystological confirmation. Bilateral mastectomy was performed and medical therapy with bromocriptine 10 mg/day was started. After 2-year follow-up the patient is disease-free. Hormonal, neuroradiological and oncological patterns are all negative or markedly improved. We stress the importance of prolactin for its possible biological effects on breast cancer induction or growth. Moreover in any case of hyperprolactinemia we suggest a mammographic examination and, in the case of breast cancer, at least a baseline hormonal profile.
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INTRODUCTION

About 1% of breast neoplasms is male breast cancer (1); bilaterality accounts for 1.5-2% of such cases (2, 3); synchronousness is an exceptional feature (4). High levels of estrogen, low levels of androgen, Klinefelter's syndrome and hyperprolactinemia are widely accepted as of primary importance within the spectrum of risk factors for this condition. Egyptian males are at higher risk from this cancer because of hepatic fibrosis secondary to chronic schistosomal infection and relative increase of estrogen (3).
Unfortunately the relative rarity of this cancer has not allowed enough *in vivo* studies to assess its real hormonal profile.
We describe an unusual association of a PRL-secreting pituitary macroadenoma synchronous with bilateral breast cancer in a young man. To our knowledge only 3 cases of such association have been previously described (2, 5, 6). This is the first one in which both pituitary and breast tumors are found together at the time of presentation.

CASE REPORT

A previously healthy 45-yr-old Caucasian male presented at the end of May 1997 because of marked obesity (BMI 39.8), gynecomastia and bloody secretion from the right nipple. His past pathological history was unremarkable except for increasing weight gain over the previous 5 yr. He had stopped smoking 5 yr before and was currently taking no medication nor consuming alcohol. He had fathered a daughter 8 yr before. Because of increasing bilateral breast size, he had recently used a mechanical vibrator for a short time in an attempt to reduce breast volume. A bloody secretion from the right nipple appeared one month prior to our observation and cleared without treatment; for this reason no sample for analysis was obtained. A mammography disclosed numerous small, irregu-

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lar and dismorphic bilateral calcifications, prevalent on the left side, highly suspected for neoplastic pattern. The patient was then admitted to the Department of Surgery for hystologic confirmation.
On physical examination the patient was found to be obese (BMI 39.8), without loss of secondary sexual characters. No headache or visual disturbances were present. Both breasts were enlarged, with small firm bilateral nodules about 1 cm in diameter palpable just under the nipples; no secretion was seen or provoked by palpation. The rest of the examination was unremarkable.
Routine laboratory tests, carcinoembryonic antigen (CEA), Ca 15.3 and β-CG were in normal range. Hormonal profile showed the following findings: PRL 33,100 mU/l (range 40-450); testosterone 2.9 nmol/l (9.7-28.4); FSH 2.7 U/l (0.8-9); LH 1.3 U/l (2-12); plasma morning cortisol 564 nmol/l (140-700); TSH 2.1 mU/l (0.2-5), free T_4 (FT_4) 9 pmol/l (8-19); GH 1.0 ng/ml (1-5); 17-β-E2 175 pmol/l (30-130). PRL, 17-β-E2 and testosterone levels were further controlled on two separate occasions and confirmed the previous results. The patient was not considered to be suffering from Klinefelter's syndrome because he had fathered a daughter, his gonadotropins were in low/normal range and both testes were normal in size.
Chest X-ray, electrocardiographic pattern and ecographic study of the upper abdomen and testes were all negative except for a mild liver steatosis and a low-degree left hydrocele. A skull X-ray revealed marked bone erosion of clinoids and *dorsum sellae*, and partial destruction of sellar floor, particularly on the right side. A sellar high-resolution computed tomography (CT scan), performed with iv administration of contrast material, disclosed a wide intrasellar hyperdense macroadenoma (more than 2 cm in diameter) with widening of *cavum sellae*, diffuse bone erosion and destruction of the floor particularly on the right side. In view of the hormonal profile, the lesion was assumed to be a macroprolactinoma. An ophthalmologist did not disclose visual field defects on the basis of clinical and instrumental examination.
Hystological examination of excisional biopsies of both breasts (Fig. 1A and 1B) revealed:
1) right breast biopsy (6x4 cm macroscopically) – microfoci of intraductal breast cancer, G2, with cribriform and papillary pattern; positivity (>30%) for estrogen and progesterone receptor (clones 6F11; clones hPRa2 and hPRa3, respectively); Ki-67 was negative at a rate of 2%; p53-protein expression was negative;
2) left breast biopsy (6x5 cm macroscopically) – infiltrating ductal carcinoma, G2, with extensive intraductal component G1, with cribriform and papillary pattern - pT1a (0.2 cm in diameter); positivity (80%) for estrogen and progesterone receptor (clone 6F11; clones hPRa2 and hPRa3, respectively); Ki-67 was negative at a rate of 5%; low expression (2%) of p53-protein.

The patient underwent bilateral mastectomy according to Patey's technique; no residual tumor or lymph nodal involvement was found on hystological examination. A total-body radionuclide bone scan was negative. On the fifth day post-operation the patient was discharged while taking 10 mg/day bromocriptine, and was advised for a close follow-up. Hormonal profile is described in Table 1 (baseline levels and 24 months of follow-up).
A sellar CT scan was repeated at 6, 12 and 24

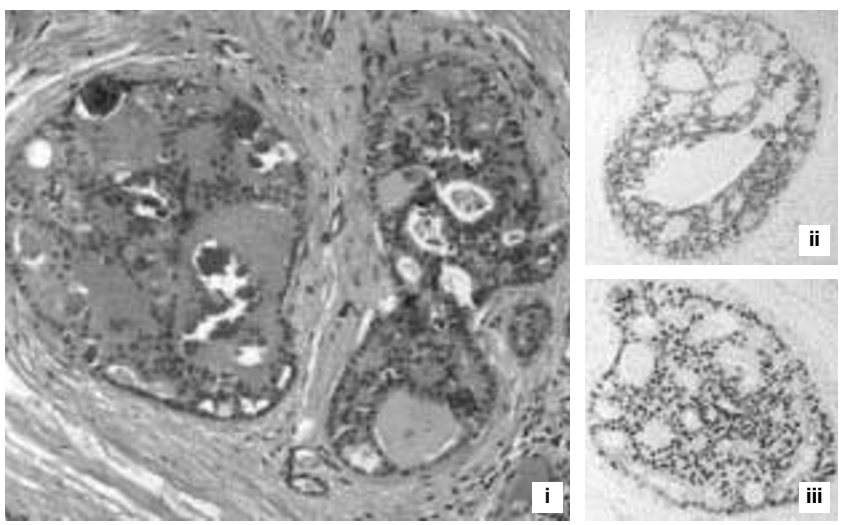

Fig. 1A - *Right breast biopsy; intraductal carcinoma with cribriform pattern - G2 - EE 40x (i); estrogen receptors (ii); progesterone receptors (iii).*

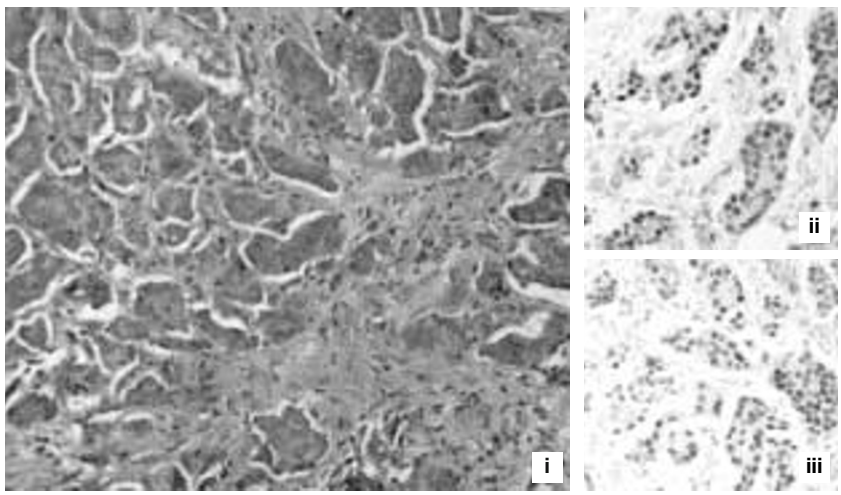

Fig. 1B - *Left breast biopsy; infiltrating ductal carcinoma - G2 - EE 40x (i); estrogen receptors (ii); progesterone receptors (iii).*

months of follow-up; a marked reduction of hyperdensity and dimensions of the macroadenoma was noted (Fig. 2). Physical examination, chest X-ray, radionuclide bone scan, CEA, Ca 15.3 and ecographic study of upper abdomen performed at 6, 12 and 24 months of follow-up were also negative; the BMI fell to 33.2.

DISCUSSION

Though exceptionally rare, male breast cancer is being increasingly recognized especially in established predisposing conditions. Bilateral cancer has been previously described only in three cases (2, 5, 6). In all cases hyperprolactinemia was simultaneous or preceded the time of tumor diagnosis. Moreover in all cases low levels of androgens and/or high levels of estrogen were noticed.

Apart from lobular carcinoma, male breast cancer is histologically similar to female (7). Disease stage is usually more advanced in men than in women, because of a more rapid skin and nodal involvement (more than 60% of cases are diagnosed in stage 2, 3 or 4).

Among the risk factors the most widely accepted ones are:

1) high levels of estrogen and/or low levels of androgen (whether or not associated with high levels of PRL). In a previous study (8) 17 men with breast cancer showed levels of estrone and 17-β-E2 higher than a control group. Estrogen, when used for prostate cancer, can induce breast cancer (9). Absolute or relative high levels of estrogen seem to be the rate-determining factor in inducing gynecomastia. It is of note that most cases of gynecomastia are idiopathic; the other ones depend on drugs, hepatic liver cirrhosis, malnutrition, hypogonadism, kidney diseases and hyper/hypo-thyroidism (2);

Table 1 - *Hormonal profile of the patient; baseline and follow-up values during bromocriptine therapy 10 mg/day.*

	PRL (40-450 mU/l)	Testosterone (9.7-28.4 pmol/l)	17-β-E2 (30-130 pmol/l)	FSH (0.8-9 U/l)	LH (2-12 U/l)	TSH (0.24-5 mIU/l)	Free T_4 (7.7-22 pmol/l)	GH (1-5 ng/ml)	Cortisol (135-690 nmol/l)
Baseline	33,100	2.9	175	2.7	1.3	2.1	9	1.0	564
1 month	5250	5.2	110	2.1	1.5	1.6	12.3	-	-
3 months	980	8.7	95	1.7	1.3	2.0	14.3	-	580
6 months	230	12.8	50	1.9	1.0	0.9	10.5	-	620
12 months	161	15.1	42	1.6	1.3	2.1	11.6	1.0	660
18 months	310	21	48	1.9	1.2	1.5	14.3	1.1	-
24 months	195	22.1	45	2.4	1.6	1.8	16.9	1.2	610

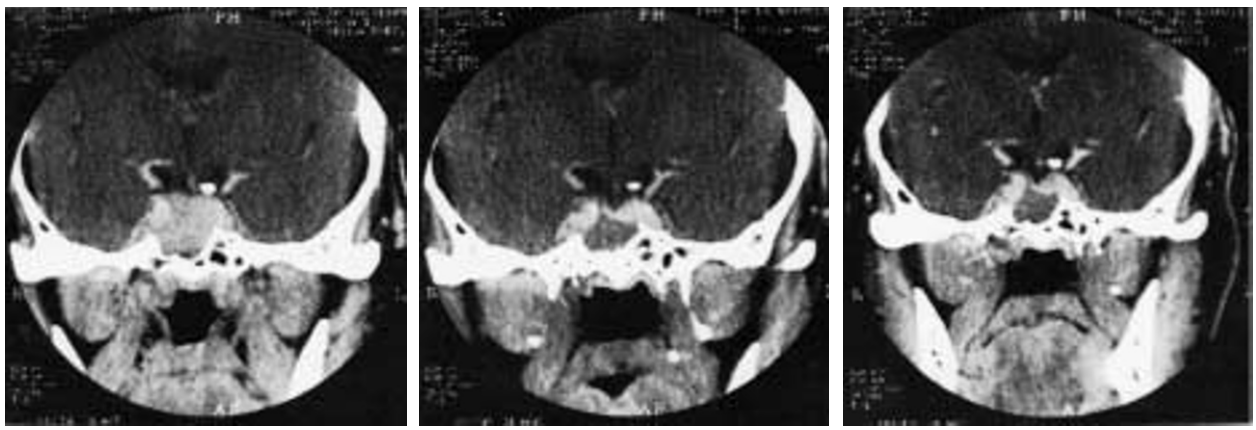

Fig. 2 - *Neuroradiological findings of the pituitary macroadenoma on computed tomography scan; baseline and follow-up imaging after 12 and 24 months (left to right).*

2) Klinefelter's syndrome: a relatively frequent condition characterized by primary hypogonadism, infertility, typical chromosomal pattern (47 XXY), with a 20-times relative-risk of breast cancer greater than for normal men (10);
3) hyperprolactinemia: *in vitro* studies largely demonstrate that PRL and E2 are the most important stimuli for breast cancer growth in humans (11). PRL seems to stimulate both stromal and epithelial cells leading to secretion of local growth-factor(s) which create a mitogenic background for uncontrolled cell proliferation (12). In a control study (1), Olsson and Ramstam noticed that most of the patients suffering from breast cancer had head trauma, skull fractures or had been taking hyper-PRL-inducing drugs in the past years and all had gynecomastia. High PRL levels were due presumably to pituitary stalk trauma with decrease of inhibitory hypothalamic dopaminergic tone on adenohypophysis (13, 14).

Previous experiments on mice show that PRL possesses a marked tumorigenic effect on breasts (15). Controversial, on the other hand, seems to be such association in humans. In fact hypophysectomy, bromocriptine and other therapies used to reduce PRL levels are totally ineffective in controlling breast cancer growth (16). Some authors hypothesized a sort of mammalian autocrine/paracrine cycle of PRL regulation. This finding was based on two observations. Firstly, in some hypophysectomized subjects PRL is not totally abolished from plasma circulation (in contrast with other pituitary hormones), suggesting some other source of secretion of PRL itself. Secondly, an extra-pituitary synthesis and/or secretion of PRL has already been demonstrated in human T-lymphocytes and *decidua* (16). Breast tissue itself, both normal and malignant, is a well-recognized source of extra-pituitary PRL (17). Recently some authors have shown that N-terminal fragment (16 kDa) of PRL is a potent stimulator of angiogenesis, essential for neoplastic growth. Moreover a significant difference in the expression of PRL receptor between intra- and extra-tumoral stromal tissue, in favor of extra-tumoral one, suggests a sort of intratumoral down regulation of such receptors. These data demonstrate that PRL and PRL-receptor complex can be found in the vast majority of human breast cancer, even in presence of estrogen or progesterone receptors (16).

IGF-I is a potent mitogen *in vitro* and most human breast cancers contain receptors for IGF-I, often over-expressed and co-expressed with estrogen receptors (18). The relationship between PRL, IGF-I and IGF-I receptor still remains matter of debate, as well as its prognostic implications. PRL may induce IGF-I secretion from hepatocytes (19); IGF-I, on the other hand, is a potent and specific secretagogue of PRL release in vertebrates (20), and may enhance PRL secretion in human prolactinomas *in vitro* (21). Normal mammary tissue is also able to synthesize and secrete IGF-I (22). Activation of PRL receptor is sufficient for induction of mammary carcinomas in mice, while activation of the GH receptor is not sufficient for mammary tumor formation (23). Moreover some authors showed that a rise in PRL after mastectomy is associated with a fall in serum IGF-I through a diminished secretion of breast tissue IGF-I (24).

In conclusion, the characterization of the PRL system (receptors, enzymes, etc.) in the tissues from

any case of male breast cancer and the comprehension of its relationship with local and systemic hormones and growth factors, might give important information on the interactions between PRL and tumor induction and/or growth. Genetic alterations at the level of proto-oncogenes as well as of tumor suppressor genes would also be worth investigation of their prognostic significance.
The above data clearly suggest a relationship between PRL and breast cancer; unfortunately the relative rarity of the association between this cancer and hyperprolactinemia has not allowed enough *in vivo* studies to determine whether PRL is a causative agent of breast cancer *per se*. On the other hand, the present case report further supports a role for PRL in inducing breast cancer. Therefore, we recommend an accurate physical examination and a bilateral mammographic study in any case of hyperprolactinemia (especially prolactinoma). Conversely, in the presence of unilateral or bilateral breast cancer we think it is mandatory to perform at least a complete baseline hormonal profile. These simple rules might lead to a prompt diagnosis, a faster control of hyperprolactinemia and improvement in the prognosis of breast cancer.

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