Breast Cancer in a Young Female with Antipsychotic-induced Hyperprolactinemia: A Case Report

Jareer H. Abu Hmeidan¹, and Arief I. Arrowaili²

¹Department of Surgery, Prince Mohammed Bin Abdulaziz Hospital, Riyadh, Saudi Arabia
²Department of Surgery, Al-Imam Muhammad Ibn Saud Islamic University School of Medicine, Riyadh, Saudi Arabia

Abstract

Introduction: The relationship between prolactin (PRL) and breast cancer in humans has been a controversial issue for a long time. Although some animal and human in vitro studies illustrated an undeniable effect of PRL in inducing and promoting mammary cancer, epidemiological studies have been less conclusive. There have been few reported cases of breast cancer in patients with hyperprolactinemia due to prolactinoma.

Case Presentation: We present a case of bilateral, multifocal, metastatic, triple negative breast cancer in a 33-year-old female with long-standing, antipsychotic-induced hyperprolactinemia.

Conclusion: There is a growing body of evidence on the carcinogenic effect of prolactin on mammary tissue. Studying tumor biology in patients with long standing hyperprolactinemia might prove useful in delineating the relationship between PRL and breast cancer in humans.

Keywords: breast cancer; prolactin; anti-psychotics

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Consent: We confirm that the patient has given the informed consent for the case report to be published.

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*Correspondence to: Jareer H. Abu Hmeidan, Department of Surgery, Prince Mohammed Bin Abdulaziz Hospital, Riyadh, Saudi Arabia; Email: hmeidanj@pmah.med.sa
Introduction

Unlike estrogen, the role of PRL in the development of breast cancer in humans has not been well defined. Nevertheless, there is accumulating evidence on the carcinogenic effects of hyperprolactinemia on mammary tissue from animal and human in vitro studies, and to a lesser extent from some epidemiological studies. Daniels et al. first reported a case of breast cancer in a patient with prolactinoma in 1976 [1]. Since then, eleven more cases were reported in both male and female patients who had breast cancer and prolactinoma [2-11]. Hyperprolactinemia was postulated to play a role in the development of breast cancer in these cases. We present a case of bilateral, multifocal, metastatic, triple negative breast cancer in a young female with long-standing, antipsychotic-induced hyperprolactinemia.

Case report

A 33-year-old female presented complaining of masses in both of her breasts. She took notice of the masses 3 months earlier owing to pain felt in both breasts, and reported a perceptible increase in the size of the masses since first noted. The patient had her menarche at the age of fifteen. She had three full term pregnancies, first of which was at the age of twenty-five, and she did not breast-feed any of her offspring. When queried, the patient stated that she did not use any form of contraception in her life. She denied any family history of breast or ovarian cancer, and she did not have any previous breast biopsies. Her past medical history was significant for a diagnosis of schizophrenia, for which she was being treated with the atypical antipsychotic Paliperidone (6mg p.o. once daily) for the past thirteen years. Treatment with Paliperidone was accompanied by hyperprolactinemia, galactorrhea, and amenorrhea for the past twelve years, and PRL levels were persistently high (2,069 mIU/L at time of presentation) despite treatment with bromocriptine (5mg p.o. once daily). A previous MRI of the sella turcica was normal. On physical exam, the Lt. nipple appeared retracted. There were multiple contiguous irregular masses involving most of the breast including the retroareolar region bilaterally. In addition, there were few palpable axillary lymph nodes bilaterally.

Bilateral mammogram revealed highly suspicious masses and scattered microcalcification on both sides. The breast parenchyma was remarkably dense, significantly reducing the yield of the exam. Breast ultrasound showed multiple hypoechoic masses with irregular outlines replacing most of the breast parenchyma (Fig.1). Contrast enhanced breast MRI showed bilateral irregular breast masses that displayed rapid contrast uptake followed by washout (Kuhl curve type III). The largest mass on the Rt. side measured 7.5cm, and the largest on the Lt. side measured 5.1cm. Masses occupied most of the breasts parenchyma, and some of the masses showed internal necrosis (Fig.2). In addition, multiple enlarged axillary lymph nodes were present. Large-core needle biopsies were obtained from both breasts and showed Scarff-Bloom-Richardson (SBR) grade II invasive ductal carcinoma (tubular score:3, nuclear score:3, mitotic score:1). A staging CT scan showed multiple enlarged supraclavicular lymph nodes bilaterally, in addition to enlarged mediastinal lymph nodes, some of which exhibited necrosis. A solitary nodule was noted in the lingula of the Lt. lung. Technicium99m MDP whole body bone scan did not detect any metastatic bone lesions. An 18F-FDG PET/CT scan of the whole body confirmed the
metastatic nature of the supraclavicular and mediastinal lymph nodes, along with the Lt. lung lesion, with the addition of a new metastatic lesion in the middle lobe of the Rt. lung that was not seen on the initial staging CT (Fig.3).

Figure 1 Ultrasound image of the Rt. breast demonstrating multiple hypoechoic contiguous masses with irregular outlines occupying most of the Rt. breast.

Figure 2 Breast MRI with contrast showing multiple bilateral enhancing irregular masses, almost replacing the whole of the breast parenchyma.

The patient received three cycles of chemotherapy. Response to treatment has been unsatisfactory so far, with less than 20% decrease in the volume of the primary tumor, and the appearance of new sub-pleural metastatic lesions in the lung.

Discussion

The relationship between antipsychotics use and hyperprolactinemia is well established. The use of any antipsychotic is potentially associated with a transient elevation in serum levels of PRL [12]. Antipsychotics that dissociate slowly from the D2 receptors result in protracted blockade of the receptors, and consequently result in greater PRL release [13]. Conversely, antipsychotics that have higher ability to cross the blood-brain barrier are more likely to occupy central (striatal) D2 receptors, leaving more pituitary D2 receptors unoccupied, and resulting in less PRL release [14].

Figure 3 Whole body 18F-FDG PET scan showing the primary breast tumors (Br), the involved axillary lymph nodes (Ax), the metastatic mediastinal lymph nodes (Med), and the metastatic lung lesions (L).
mammary cancer in rodent models, and in human \textit{in vitro} models, have been well documented. PRL has been shown to increase the growth of tumor cells, boost the development of chemically induced mammary cancer, and even induce mammary cancer in rodent models [15]. \textit{In vitro} studies of human mammary tissue have shown that prolactin receptors (PRLRs) are expressed at higher levels in breast cancer cells than in normal mammary tissue [16], and that breast cancer cells locally produce PRL that may act as a major local growth promoter via autocrine and paracrine loop mechanism [17]. PRL has been found to increase growth, inhibit apoptosis, enhance motility, and increase vascularization of human breast cancer cells cultures [15]. Antibodies that neutralize locally expressed (autocrine) PRL have been shown to result in inhibition of cell growth in such tumors [18].

From an epidemiological point of view, the largest prospective case controlled study to date of 1,500 women conducted by Tworoger et al., has shown a 30% higher breast cancer risk, which increased to 70% after measurement error correction, for the women with the highest versus the women with the lowest PRL concentrations in the study [19]. This effect was observed in both cycling premenopausal and postmenopausal women, and was independent of estradiol and testosterone concentrations. Wang et al. have demonstrated in a retrospective cohort study conducted on 52819 women who were exposed, and 55289 who were not exposed to dopamine antagonists, that the use of antipsychotic dopamine antagonists was associated with a 16% increase in the risk of breast cancer, and that the risk increased with larger cumulative dosages [20]. This increased risk was likewise observed in women who used prolactin-elevating antiemetic dopamine antagonists, but at the same time it was not observed for other types of cancer like colon cancer, pointing to the fact that the increase in risk was primarily attributable to the drug-induced elevation of PRL and its effects on mammary tissue, and not to any other carcinogenic effect of the dopamine antagonists.

It is surprising therefore, with this growing body of evidence on the role of PRL in increasing the risk for breast cancer, to find that there have been only few published reports describing breast cancer in patients with greatly elevated PRL levels, mostly in men and women having breast cancer with prolactinomas. Of the thirteen reported cases (including ours), the diagnosis of hyperprolactinemia preceded the diagnosis of breast cancer in eleven cases [1-5,7,8,10,11], with a mean interval of 16 years (range 3-36 years). Both conditions were concomitantly diagnosed in two of the cases [6, 9]. Five of the cases (5/13) were males [3,6,8,9,11], six (6/13) were patients younger than 35 years of age [1,2,4,5,7] (mean age 44 years), and four (4/13) had tumors bilaterally [3,8,9]. The hormone receptor status of the tumor was not documented in the earliest four reports [1-4], however, in the remaining nine cases, all aside from our case (8/9) expressed estrogen receptors [5-11], and in four cases (4/9), both estrogen and progesterone receptors were expressed [5,8,9].

Our case is unique in the fact that hyperprolactinemia was drug induced and not due to a prolactinoma. In addition, all of the previously reported cases with documented
hormone receptor status were positive for estrogen receptors, while our patient had a triple negative hormone receptor status. In the epidemiological study by Tworoger et al mentioned earlier, the observed positive association between high PRL levels and breast cancer was exclusive to estrogen receptor positive tumors [19]. On the other hand, Pattison et al. reported on a case of breast cancer in a male transsexual who, similar to our case, received antipsychotics and had highly elevated PRL levels, and developed triple negative Lt. breast cancer [21]. However, the patient had received cross-hormonal treatment including high dose conjugated estrogens and cyproterone acetate for more than 7 years. Cyproterone acetate can induce hyperprolactinemia, and conjugated estrogens independently increase the risk for breast cancer, making it harder to speculate on the role of the antipsychotic-induced hyperprolactinemia in development of breast cancer in this case.

One interesting direction that could be suggested in learning about the relationship between PRL and breast cancer is examining the pattern of PRLRs expression on tumor cells from patients with highly elevated PRL levels and breast cancer. A quantitative and qualitative analysis of PRLR isoforms expressed by these tumors might provide new information on the correlation between PRL and breast cancer. Such analysis might also serve to predict tumor response to anti-prolactin therapy if these tumors prove to be PRL dependent. Although the results from studies on the conventional anti-prolactin treatment in breast cancer have been contradictory and generally disappointing [22,23], the newer PRLR antagonists, that compete with locally produced (autocrine) PRL for receptor binding, might prove to be more useful, particularly in such tumors that are PRL dependent [16].

Conclusion

There is a growing body of evidence on the correlation between PRL and breast cancer from bench research and epidemiological studies. One other potential source of evidence comes from reported cases of patients with hyperprolactinemia and breast cancer. Our case is unique mainly because breast cancer was associated with hyperprolactinemia that was drug induced rather than due to prolactinoma. Quantitative and qualitative analysis of PRLRs expressed by tumor cells from such patients might provide new insight on the relationship between PRL and breast cancer.

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References

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