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Is Endogenous Prolactin, Not Endocrine Prolactin, Responsible for Hyperparathyroidism in Breast Cancer Patients?

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Breast cancer is the most common site-dependent cancer among females and the main cause of death due to malignancy in females aged 40-44 years. This illness is responsible for 33% of all gynecological malignancies and 20% of all females' mortality. According to the reported statistics in the USA, the probability of developing breast cancer is one in every 8 women.[1]

Hypercalcemia in patients with breast cancer is generally considered a result of osteolytic metastasis or circulating tumor derived products. In such situations, severely depressed plasma parathormone (PTH) is expected.[2,3] Hypercalcemia in malignancies is multifactorial, and results from a combination of increased bone resorption associated with decreased renal excretion of the increased extra-cellular fluid calcium.[4] One of the most frequent etiologies of hypercalcemia is hyperparathyroidism which is usually neglected in breast cancer patients, while recent studies have shown increased incidence of primary hyperparathyroidism in breast cancer patients regardless of clinical staging or anti-tumor therapy.[2]

Plasma parathormone and breast cancer

PTH-related peptide (PTHrP) has a high homology with the N-terminal portion of PTH, which is capable to act with PTH through common as well as specific receptors. In physiological circumstances, PTHrP is produced locally in many normal tissues and has both autocrine and paracrine functions. One of these circumstances is embryonic cells growth development and pregnancy period. PTHrP has an endocrine role in the bone and kidney. As a fact, PTHrP is considered the main reason for hormonal hypercalcemia in malignancies; therefore, the PTHrP plasma level is believed to be a conformational diagnostic test in 80% of breast cancer patients.[5,6]

PTHrP, as well as PTH, causes an increase in the plasma level of calcium and a decrease in the plasma level of phosphorus. In physiological conditions, increased plasma levels of calcium cause a decrement in PTH secretion while in breast cancer patients - with no vitamin D metabolism pathway or digestive disorder- the PTH plasma level is not reduced as a result of hypercalcemia, and has a higher plasma concentration in comparison with the normal population.[2,3]

Prolactin and breast cancer

Prolactin is a lactogenic hormone produced by the pituitary gland. Prolactin induces terminal differentiation in breast epithelial cells and plays a role as a growth and survivor factor.[7] Hyperprolactinemia in breast cancer leads to faster growth in cancerous cells, and is associated with a higher risk of metastasis and poor prognosis.[8, 9] These findings are more significant in cases with positive estrogen and progesterone receptors.[9-11]

Previous studies have shown plasma levels of prolactin in breast cancer patients are higher in comparison with the healthy population and also patients with other cancers.[11-13] This finding is more significant in postmenopausal women rather than premenopausal and is confirmed in animal studies.[9-14]

One study has reported a significant association between the plasma level of prolactin and PTHrP mRNA expression in the breast tissue.[4] There are some evidence about increased plasma levels of prolactin in both primary and secondary hyperparathyroidism.[15] Another study has shown the inductive role of prolactin concentration dependent secretion of PTH

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in parathyroid cells.[16]

Endocrine prolactin and endogenous prolactin in breast cancer

Considering the existing evidence on the role of prolactin in the pathogenesis and progression of breast carcinoma, various studies have not reached an agreement to blame prolactin to date. Most of the studies have evaluated endocrine prolactin secreted by the pituitary gland, but there is still less attention to endogenous prolactin produced by breast cancer cells.[17] Although prolactin and prolactin mRNA are detected in the breast tissue, their role is still not clearly defined.[18] In addition, the existence of a cycle between endogenous prolactin and prolactin receptors in basal cell carcinomas (BCCs) would make all the medication plans according to endocrine prolactin fail.

Considering this point is very important when a high percentage of breast cancer patients have hyperprolactinemia which is associated with the tumor size and the risk of recurrence and metastasis, i.e. a poorer prognosis.[19] PTH secretion due to prolactin stimulation occurs within one hour and rises during 3 hours, and seems to be effective in calcium homeostasis by this way.[16] Hypercalcaemia in such situations should suppress PTH. In breast cancer patients, not only the reasons mentioned earlier, but also PTHrP via the mentioned pathway should help to reduce the PTH plasma level. However, most of the studies in this field have reported findings contrary to what is expected. This finding, according to the discussed evidence, might suggest the stimulating effect of prolactin. Few studies have been done to clarify the relationship between PTH and PTHrP, and there is still no conclusion on any diagnostic or prognostic value of the changes of PTH or PTHrP fragments in breast cancer patients.

There is some evidence on a direct correlation between the plasma level of PTH and prolactin in primary and secondary hyperparathyroidism, and in the existence of hyperprolactinemia, plasma level of PTH is increased as well.

The plasma level of prolactin is higher in breast cancer patients in comparison with the normal population or patients with other solid tumors. Hyperprolactinemia in breast cancer patients leads to the faster growth of cancerous cells and a larger tumor size, higher risk of recurrence or metastasis, and a poor prognosis.

On the other hand, hyperparathyroidism aggregates hyperprolactinemia; recent studies have also proved the secretion of prolactin by breast cancer cells (endogenous prolactin).[20,21] This finding confirms the reason for hyperprolactinemia in breast cancer patients with previous hypophysectomy.[22] This point explains why of the according endocrine prolactin medical plans in breast cancer patients are going to be failed. In addition, we should consider the new demand of breast cancer patients for early diagnosis of hyperparathyroidism. If the increased level of prolactin is an alarme sign to treatment failure of metastasis or recurrence of breast cancer, prolactin can be defined as a new tumor marker of breast cancer.

As a summary, beside the generally accepted mechanism of hypercalcemia caused by PTHrP, we suggest PRL as an aggregating factor of hypercalcemia via stimulating the PTH production, which makes PTHrP unable to suppress PTH by elevated serum calcium levels, and elevated PTH can be a trigger for aggregation of hyperprolactinemia. As stated earlier, this vicious cycle can be considered in breast cancer patients, which can be responsible for the highest serum PRL level in breast cancer patients among solid tumors.

In order to examine our theorem, studies should be designed to evaluate the serum level of prolactin, as well as breast tissue concentration of prolactin in breast cancer patients simultaneously. In addition, the serum level of PTH should be compared with patients with benign breast disease and hyperparathyroidism to find out whether the increased serum level of PTH and prolactin is associated with breast tissue prolactin production. It is recommended to consider the difference in the serum level of prolactin and PTH in breast cancer patients in comparison with the patients with benign breast diseases and hyperparathyroidism. The authors suggests to follow up breast cancer patients, which allows them to screen and detect hyperparathyroidism in early stages.

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