Two Birds With One Stone: Octreotide Treatment for Acromegaly and Breast Cancer

Case Report

A 74-year-old woman presented to the Breast Medical Oncology clinic for treatment of hormone receptor–positive, human epidermal growth factor receptor 2 (HER2) –negative, metastatic invasive lobular carcinoma (ILC). She was initially diagnosed in January 2007 with left breast ILC, which was estrogen receptor (ER) positive, progesterone receptor positive, and HER2 negative, when she presented with an ulcerating left breast mass. She underwent a left modified radical mastectomy and was found to have a pathologic stage T4N0 tumor. She received adjuvant chemotherapy with cyclophosphamide, methotrexate, and fluorouracil for six cycles followed by adjuvant therapy with exemestane at an outside hospital. Two years after the initiation of exemestane, she complained of bilateral hip and shoulder pain, and in April 2010, when a bone scan revealed multiple areas that were consistent with osseous metastasis, she presented to our center (M.D. Anderson Cancer Center) for additional treatment.

The patient had a remote history of acromegaly that was treated with transsphenoidal resection in 1991, with no additional follow-up care. She also had a history of poorly controlled type 2 diabetes mellitus, hypertension, and osteoarthritis. On evaluation the patient was found to have numerous skin nodules that were suggestive of metastasis and features that were suggestive of acromegaly (Figs 1A and 1B).

A biopsy of her skin nodules revealed metastatic carcinoma consistent with breast origin that was ER positive, progesterone receptor positive, and HER2 negative. A staging work-up with a computed tomography scan of the chest/abdomen and pelvis revealed diffuse bone, subcutaneous, intramuscular, pulmonary metastasis, and diffuse mediastinal lymphadenopathy. In June 2010, she was treated with fulvestrant and dasatinib as part of a clinical trial, and in October 2010,

on disease progression in the lungs, she was withdrawn from the study. At that time, a magnetic resonance imaging scan of her pituitary revealed a residual subcentimeter adenoma or residual normal glandular tissue in the anterior sella, and measurements of insulin-like growth factor-1 levels (IGF-1) and growth hormone (GH) levels were elevated at 352 ng/mL (normal range, 64 to 188 ng/mL) and 6.45 ng/mL (normal range, 0.01 to 3.61 mU/L), respectively, thus confirming the diagnosis of active acromegaly. Treatment for her acromegaly was then initiated with the somatostatin analog octreotide in October 2010. With her consent, treatment with fulvestrant was reinitiated to determine whether treating the acromegaly would help overcome endocrine therapy resistance. She demonstrated a profound and durable response with the addition of octreotide. She experienced a significant clinical improvement with the partial or complete regression of her subcutaneous tumor nodules. She also had improvement in her bone pain. Nine months after octreotide initiation, her GH declined to a nadir of 0.67 ng/mL, although her IGF-1 levels did not respond appreciably and ranged between 346 and 390 ng/mL.

Compared with her initial [^{18}F]fluorodeoxyglucose (FDG) positron emission tomography scan in June 2010, the positron emission tomography scan performed after octreotide treatment in January 2011 demonstrated a marked interval decline in the FDG-avid metastatic disease, as shown in Figures 2A and 2B. Cancer antigen 27-29 levels decreased from 929.2 U/mL to 299.6 U/mL after initiation of octreotide (Fig 3).

After the significant response, the disease remained stable, but at 14 months the patient was found to have progression, with a malignant pericardial effusion that required a pericardiocentesis. Notably, the patient had also missed 5 months of octreotide treatment. During this period, the GH peaked at 1.84 ng/mL and IGF-1 rose to 447 ng/mL. Interestingly, the GH levels seemed to correlate with her disease course. The timing of cancer progression coincided with the

Fig 1.

Fig 2.

period when she was not taking octreotide and her GH and IGF-1 levels rose from nadir.

Discussion

This is the first case report, to our knowledge, documenting that the treatment of acromegaly has a potential therapeutic effect on breast cancer. Acromegaly is characterized by a sustained elevation of circulating GH and IGF-1. A diagnosis of acromegaly has been associated with metabolic disturbances (diabetes mellitus, hypertension),¹ and potentially an increased risk of cancer, including breast cancer.² However, the current epidemiologic data remain inconclusive, largely because of the limited number of cases of untreated acromegaly in the general population.² Interestingly, the preclinical data seem to strongly support a role for the GH/IGF pathway in mammary tumorigenesis.^{3,4} This pathway plays a vital role in the development of the normal mammary gland.⁴ In fact, mammary gland development does not occur in the absence of GH and/or IGF-1.³

The IGF signaling pathway includes the peptide ligands IGF-I, IGF-2, and insulin. IGF-1 secreted by the liver, which is primarily

regulated by GH, is the main source of circulating IGF-1 levels. However, other sources of extrahepatic IGF-1 and IGF-2 secretion also contribute to circulating IGF levels.⁵ The IGFs exert their effects primarily through binding and activation of the tyrosine kinase receptor IGF-1 receptor (IGF-1R).⁶ GH and IGF-1R have been shown to act as transforming oncogenes in mammary epithelial cells.⁷ Their overexpression in breast cancer cells promotes a more aggressive phenotype with increased metastatic potential.⁸⁻¹⁰ This effect can be reversed by blockade of GH receptor (GHR) or IGF-1R.³ IGF-1R is overexpressed in breast cancer and its activation has been linked to poor prognosis in ER-positive breast cancers in humans, suggesting that the GH/IGF axis may be important in endocrine resistance.¹⁰⁻¹² Furthermore, recent preclinical data suggest that coinhibition of both ER signaling and IGF signaling in breast cancer can overcome endocrine resistance.¹³ Our patient had elevated GH/IGF-1 levels and conversely may have had activation of the IGF-1R signaling pathway. Her tumor (malignant pleural effusion) had evidence of IGF-1R expression by immunohistochemistry (IGF-1R β , 1:500; Santa Cruz Biotechnology, Dallas, TX), confirming the presence of the receptor (Figs 4A and 4B, arrow). She was also found to have rapidly growing, metastatic, ER-positive breast cancer with clear progression on previous endocrine therapy with an aromatase inhibitor (exemestane) and an estrogen receptor down regulator (fulvestrant). The addition of octreotide to her treatment and, conversely, the decrease in her GH levels were associated with a dramatic improvement in her disease, despite the fact that she

Fig 3.

Fig 4.

continued to receive the same systemic therapy for breast cancer (fulvestrant). This clinical case echoes the preclinical findings^{3,4} that linked the GH/IGF pathway to breast cancer proliferation and survival, and provides further rationale for investigating this pathway.

Certain questions remain unanswered in our patient's case with respect to the exact mechanism of action behind octreotide therapy. Specifically, despite a decrease in GH levels to a normal range with the use of octreotide, the patient experienced only a modest decrease in IGF-1 levels. In fact, these never reached normal range. However, the patient still seemed to derive a therapeutic benefit from the addition of octreotide. One can hypothesize that the potential response to treatment may be partly a result of decreases in IGF-1 or a direct consequence of decreases in GH levels and, conversely, decreased activation of GHR. Interestingly, the GHR has been shown to drive mammary tumorigenesis in preclinical models.¹⁴ Another potential mechanism of action is through decreases of another IGF ligand, IGF-2. IGF-2 has also been implicated in activation of IGF-1R,⁵ and IGF-2 overexpression has been linked to the development of ER-positive breast cancer.¹⁵ Unfortunately, IGF-2 levels were not monitored in our patient, given that these are not routinely monitored in the management of acromegaly.

Our patient case also raises the question of the exact role that octreotide can or should play in breast cancer treatment. Previously, clinical trials examining the addition of octreotide to endocrine therapy in the adjuvant setting, and as a single agent in the metastatic setting, failed to show any benefit.^{16,17} These trials, along with our patient case, stress the importance of understanding the exact mechanisms behind the GH/IGF signaling pathway and breast cancer. Perhaps more specific targeting of the receptors or ligands will be a more useful strategy.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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