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A Raloxifene Withdrawal Response: Translational Research, Definitions, and Clinical Applications

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Lemmo[1] contributes an interesting case report of a patient with estrogen receptor (ER) and progesterone receptor (PgR)–positive breast cancer, who was successfully treated, off label, with adjuvant raloxifene (60 mg daily) for 8 years until recurrence (ER/PgR-positive disease). This clinical case provides an unanticipated opportunity to revisit the biological rules of anti-estrogenic (aromatase inhibitors, tamoxifen and raloxifene) therapy, the manifestation of acquired resistance and the "withdrawal response." This is an important topic for the clinician. Breast cancer has the highest incidence of all cancers in women but the ER target has been the conduit for achieving the highest success in cancer therapeutics above all others.[2]

As a result, and to build upon success, it is important that efforts to integrate clinical observations with advances in understanding the mechanisms of acquired anti-hormone resistance, remain a priority to further aid patient survival.

The clinical use of the phrase "withdrawal response" was promoted through the 1950s and 1960s until the 1970s, to describe the paradoxical pharmacology of high-dose synthetic estrogen therapy, that is, diethylstilbestrol (DES), when used for the treatment of metastatic breast cancer (MBC), in women more than 5 years following their menopause.[3] Thirty percent response rates were routine, but when recurrent tumor growth resumed, withdrawal of the DES therapy caused a second tumor regression or a "withdrawal response." The synthetic estrogen was now fueling tumor growth. With the advance of tamoxifen in the 1970s,[4] which replaced high-dose DES therapy, clinicians again observed 30% response rates in MBA by blocking estrogen action. However, a "withdrawal response" was rarely observed (although one small series was published[5]). The reasons for this apparent failure with tamoxifen to produce a "withdrawal response," when it was commonly observed for DES with MBC patients titrated on and off treatment, was not that it did not exist, but instead the pharmacokinetics of tamoxifen were radically different than high-dose DES therapy, and the mechanism of acquired resistance was different.

High levels of tamoxifen and metabolites accumulate in the body and are retained for slow excretion over months after stopping treatment. By contrast, DES is completely excreted within days. Be that as it may, the actual explanation is far more complex when acquired resistance develops with tamoxifen. Laboratory studies with ER-positive breast cancers, retransplanted into tamoxifen treated animals for a decade, show several unique features not seen with any other cancer medicine.

Acquired resistance to tamoxifen develops under laboratory conditions in vivo within 2 years. This is consistent with the treatment of MBC. In the laboratory, breast tumors were discovered to grow because of tamoxifen treatment not despite tamoxifen treatment.[6,7] The reason that no "withdrawal response" is seen with tamoxifen when treatment is stopped is because tamoxifen remaining in the patient's body continues to stimulate tumor growth for many months. However, if this is the novel mechanism of acquired resistance to tamoxifen, seen clinically, the laboratory observation now created a conundrum: "If tamoxifen fails to control MBA and experimental tumors for no longer than 2 years, how is adjuvant tamoxifen able to control recurrence of breast cancer, with 5 years of treatment?"[8,9] The answer lies in the evolution of acquired resistance in cell populations, observed during the retransplantation into tamoxifen treated athymic mice for a decade.[10] The tamoxifen-treated tumors evolve their cell populations through selection pressure to expose a vulnerability, after 3 to 4 years: estrogen-induced apoptosis. Tumor regression occurs with physiologic levels of estrogen, after tamoxifen treatment is stopped.[11,12] Recent data with acquired anti-hormone resistant breast cancer cells in vitro illustrate how population can change within just a few months under

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selection pressure. Cells with acquired anti-hormone resistance can change from aromatase and selective estrogen receptor modulator (SERM) resistant to become estrogen or SERM-stimulated,[13,14] just like the aythmic mouse model[6] and MBC.[5] Overall, this was thought to be a unique form of acquired resistance for tamoxifen, that is, tamoxifen-stimulated tumor growth, until the same form of acquired resistance, was found for raloxifene in both cell culture and athymic animal studies,[15,16] and now clinically in this case report.[1] Unlike tamoxifen, the polyhydroxylated raloxifene does not accumulate and is rapidly excreted within days. The "withdrawal response" following raloxifene-stimulated growth in the patient occurs because the medicine is excreted rapidly, to prevent growth but there is another cytotoxic component.

During the past 20 years, a hypothesis has emerged that a woman's own estrogen causes estrogen-induced apoptosis, following the cessation of long-term (5 years or more), adjuvant anti-hormone therapy.[10,11,17] This hypothesis, and supporting laboratory data,[11] provides a cytotoxic mechanism to explain the decreases in mortality after long-term tamoxifen is stopped.[8,9] What would be anticipated when the anti-estrogen tamoxifen was stopped, if estrogen-induced apoptosis of vulnerable cells did not occur, would be estrogen-stimulated recurrences, and death in patients once adjuvant therapy stops.

It seems to be a fact of cancer biology in patients that 5 years or more of estrogen deprivation is required to transform cell populations that initially grow with estrogen to become those that die with estrogen. Estrogen-deprivation can be achieved in many ways clinically: (*a*) 5 years after menopause is required for high-dose DES to treat MBC sucessfully[18]; or (*b*) 10 years after menopause, in the estrogen alone trial of the Women's Health Initiative, that produces a decrease in the incidence of breast cancer and an increase in survival from breast cancer[19]; or (*c*) the exhaustive treatment of MBC with anti-hormone therapies for over 5 years so that estrogen, now produces a 30% response rate[20,21] and does not produce growth. This clinical concept is replicated and supported by estrogen deprivation for breast cancer cells in culture,[22,23] and SERMs therapy (tamoxifen and raloxifene) for up to a decade observed in studies with aythmic mice.[15,16]

The large body of translational laboratory research, along with consistent clinical results, implicate long-term estrogen deprivation as the key to the subsequent cytocidal action of estrogen that has created a rule for cancer biology, which now is followed by the patient case report.[1] The postmenopausal patient received 8 years of adjuvant raloxfiene treatment prior to an ER/PgR-positive recurrence. The steady and persistent shrinkage in monitored hepatic metastasis mimic animal studies with estrogen-induced apoptosis, and supports the aforementioned clinical experience with estrogen in estrogen-deprived populations,[15,16] to produce the long-term decreases in CA-15-3 (figure 1 in the case report).[1]

We must thank Dr Lemmo for contributing an important new piece to the cancer biology puzzle of the "withdrawal response." This clinical observation further helps decipher the paradox of estrogen-induced apoptosis as a general principle to aid and enhance patient care.[24]

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Anti-Estrogen Withdrawal Effect With Raloxifene? A Case Report

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Abstract

A 66-year-old patient presented with acute recurrent metastatic estrogen and progesterone receptor–positive, Her-2/neu-negative breast cancer, bone lesions (lumbar spine, pelvis), pulmonary nodules, hepatic metastasis, elevated cancer antigen 15 and liver enzymes, dyspepsia, and diarrhea. The patient had been taking raloxifene for approximately 8 years. After discontinuation, clinical parameters and symptoms improved rapidly without oncological therapy or other forms of treatment. Three months after raloxifene discontinuation, capecitabine was initiated by the treating oncologist who deemed an anti-estrogen withdrawal effect (AEWE) implausible. However, the lasting regression was more indicative of a raloxifene rebound effect than chemotherapy or other interventions. Today, the patient is asymptomatic with a good performance status. Hepatic metastatic regression has been confirmed, without any oncological treatment administered in the past 16 months and approximately 23 months following the withdrawal of raloxifene. This case highlights the need to screen breast cancer patients for the possibility of an AEWE if they are using raloxifene and possibly similar selective estrogen receptor modulators (SERMs) which includes tamoxifen, when diagnosed with advanced breast cancer, especially in the recurrent disease setting.

Keywords

breast cancer, raloxifene withdrawal, anti-estrogen withdrawal effect (AEWE), tamoxifen, naturopathic oncology, selective estrogen receptor modulator (SERM), raloxifene rebound, acquired anti-estrogen resistance

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Case Description

This case report concerns a postmenopausal patient of European descent who was diagnosed in 2005 at age 57 years with a left 16-mm localized pT1c pN1A, grade II, lymphovascular invasion +, estrogen/progesterone receptor–positive, Her-2/neu-negative breast cancer with 2/15 positive lymph nodes. She subsequently underwent lumpectomy and a six-course treatment with adjuvant chemotherapy that included 5-fluorouracil, epirubicin, and cyclophosphamide (FEC-100). The patient declined radiation therapy. Aromatase inhibitors (AIs) were not attempted due to a history of osteoporosis and concerns by the patient. In 2006, raloxifene 60 mg once daily was considered versus tamoxifen. Raloxifene, belonging to the same selective estrogen receptor modulator (SERM) category as tamoxifen in conjunction with its osteoporosis benefits, was initiated as an experimental adjuvant treatment, which turned out to be well tolerated by the patient. Her treating oncologist had retired in 2011 and refills for raloxifene were continued by a family physician and osteoporosis specialist without any further oncological evaluation. Prior to the breast cancer, the patient reported a history of endometriosis in 1997 resulting in a hystero-oophorectomy. Subsequently, the use of premarin hormone replacement ensued in 1998 until the breast cancer diagnosis in 2005.

In June 2014, the patient experienced dyspepsia and diarrhea, which eventually led her to seek a medical evaluation from a family physician. The family physician originally excluded potential infectious etiologies in the stool on July 27, 2014 and subsequently suspected active hepatitis C virus (HCV) infection on September 4, 2014, which was ruled out on September 10, 2014. The laboratory investigation on September 4, 2014 also revealed an elevated ferritin and liver function tests (LFTs). The family physician also ordered an abdominal ultrasound on September 3, 2014 and follow-up contrast computed tomography (CT) abdomen/pelvis scan on

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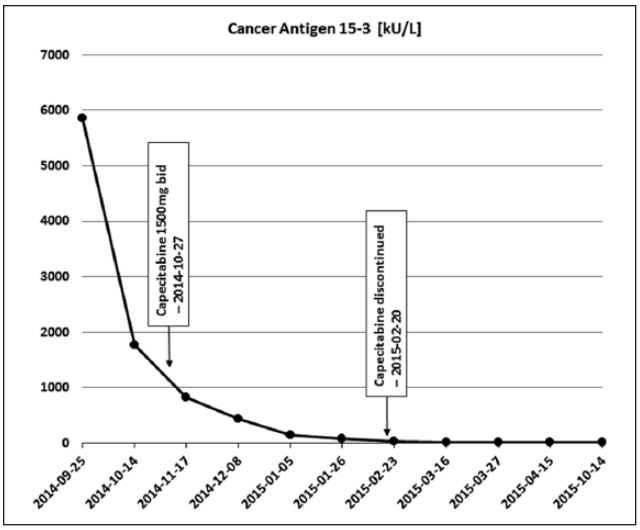

Figure 1. CA 15-3 versus time. Raloxifene had been discontinued in July 2014.

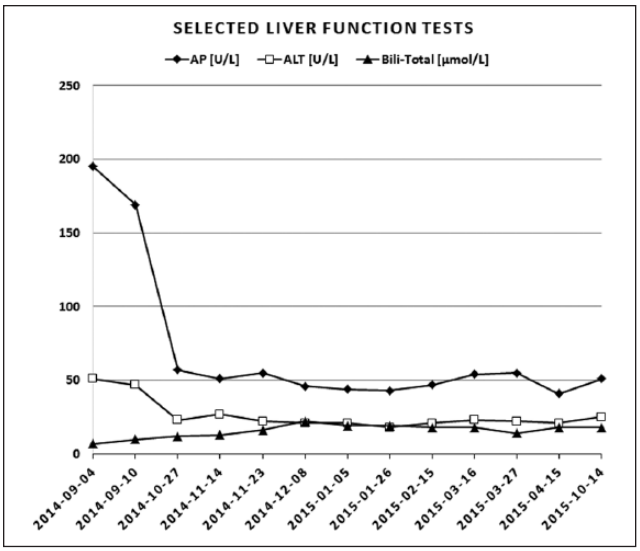

Figure 2. Liver function tests versus time. AP, alkaline phosphatase. ALT, alanine aminotransferase; Bili-Total, total bilirubin.

September 22, 2014, which noted pulmonary nodules and multiple hepatic lesions indicative of malignancy. Tumor markers ordered on September 25, 2014 revealed elevations in CA-125, CA 15-3, and CEA (Figure 1).

A referral was made to a new medical oncologist, as the original oncologist had retired, who ordered a bone scan on October 2, 2014, that revealed further evidence of metastatic disease. A liver core biopsy on October 15, 2014, confirmed hepatic metastatic disease consistent with ductal carcinoma of the breast. The biopsy also confirmed strong estrogen and progesterone receptor and negative Her-2/neu status in line with her original diagnosis back in 2005.

The patient, a retired pharmacist, had decided on her own intuition to discontinue raloxifene in July 2014 to see if there was a connection with her symptoms, in particular the diarrhea. Between this time period and October 27, 2014 (ie, within 3 months), without any oncological therapy or other forms of treatment, she experienced a significant improvement and eventual resolution of the dyspepsia along with the diarrhea, which stopped within days. LFTs also began to improve between September 4 and October 27, 2014 (Figure 2). Furthermore, the CA 15-3 tumor marker revealed truly significant reductions from 5860 kU/L on September 25, 2014, to 1772 kU/L on October 27, 2014. Notably, this effect was prior to any chemotherapeutic intervention. The tumor markers CEA and CA-125, which were also found to be elevated on September 25, 2014, were not repeated later.

On October 27, 2014, capecitabine was prescribed by the oncologist at a dose of 1500 mg twice daily. The patient ascribed the improvement in her symptoms to a possible raloxifene withdrawal effect, which was shared with the oncologist who, according the patient, viewed this as improbable. The patient, on her own volition, reduced her capecitabine dose to 1000 mg twice daily in the middle of the second cycle mainly due to the side effects of capecitabine treatment. During capecitabine treatment, continued improvements in clinical parameters were noted. The oncologist continued to opine that the positive response was solely related to the chemotherapy.

On February 10, 2015, the patient was referred to our clinic by another medical oncologist who was consulted as a second opinion. The oncologist also was unaware of a possible anti-estrogen withdrawal effect (AEWE) in breast cancer, but referred the patient to our facility to explore treatment options to help address capecitabine side effects. The patient also suffered from insomnia and anxiety and wished to explore a combined naturopathic/oncological approach. During this visit, the patient also discussed the effects of the suspected raloxifene withdrawal effect. It was psychologically distressing to her that neither oncologist seriously examined the possibility of a raloxifene AEWE. This distress along with side effects of the raloxifene withdrawal were affecting her quality of life. For the patient's symptoms, we suggested acupressure, a maitake mushroom extract and a botanical/nutritional formula reputed to assist with sleep/anxiety relief, in addition to physical activity. We had just independently discovered that one case of a raloxifene AEWE had been reported in 2004. We shared this information with the patient, which remarkably eased her psychological state. On February 20, 2015, she attempted a single infusion of vitamin C that was not repeated. Although both maitake extract and intravenous vitamin C are reported to "boost immune function" and hence may be may be

useful in adjunctive cancer therapy,[1,2] it appears unlikely that these supplements had a noticeable anticancer effect in our case, since they were initiated months after the initial dramatic decline in tumor markers, symptoms, and LFTs. However, according to the patient, these interventions were beneficial for her overall well-being.

Capecitabine was finally discontinued on the patient's own accord on February 13, 2015, without consultation from our clinic. The treating medical oncologist was not opposed to a treatment break. Along with the published raloxifene rebound case report, an upcoming family wedding had triggered this decision in an attempt to improve quality of life and enjoyment of the celebration. Interestingly, following this decision, the CA 15-3 marker continued to decline from 35 kU/L on February 23, 2015, to 15 kU/L on April 27, 2015.

Follow-up CT abdomen on April 24, 2015, compared with October 8, 2014, and December 1, 2014, revealed continued reductions in liver metastases. Chest nodules between the October and April dates were stable.

During a follow-up appointment on May 29, 2015, the patient reported continued anxiety concerns along with troublesome hot flashes and night sweats which began following the raloxifene withdrawal. She mentioned an acute gastritis episode in March requiring an emergency room evaluation that had since improved. She reported no obvious signs of disease progression. The patient had modified our recommended natural health product supplementation on her own volition in March 2015 to include a flaxseed oil capsule, vitamin D 2000 IU, B-complex tablet, and a milk thistle capsule taken all at once daily along with her morning coffee. Since the CA 15-3 marker had already declined from 5680 kU/L in September 2014 to 35 kU/L in February 2015, attribution of the patient's continued improvement to intake of this modest supplement regimen is also unlikely. She reported no other supplement use and did not receive any other therapies. She intended to continue this regime for the foreseeable future.

Follow-up CT on October 10, 2015, of the chest, abdomen, pelvis with contrast agent revealed stable pulmonary nodules and similar appearing sclerotic bony densities. Hepatic regression continued despite having discontinued capecitabine 8 months earlier. Tumor marker and LFTs as of October 14, 2015 continued to be in the normal range, with CA 15-3 at 12 kU/L, alkaline phosphatase at 51 U/L, alanine aminotransferase at 25 U/L, and total bilirubin at 18 µmol/L.

Graphic representations of the LFT results from September 2014 to October 2015 are given in Figures 1 and 2; the corresponding CT scans are shown in Figures 3 to 6. Unfortunately, no laboratory data or images predating this period were available.

As of the writing of this report (June 2016), the patient continues to do very well, is asymptomatic, and has no need of any further oncological treatment or care. It has been 16 months since the last capecitabine dose and approximately 23 months since stopping the raloxifene.

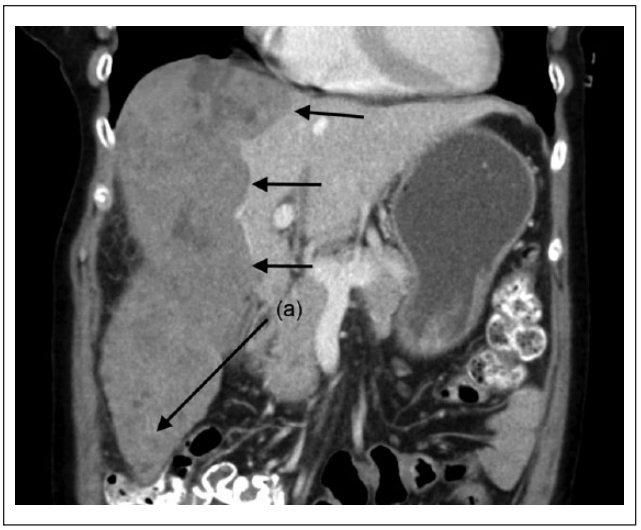

Figure 3. Computed tomography scan of September 22, 2014: Marked hepatomegaly and malignancy; liver extension into pelvic cavity (a).

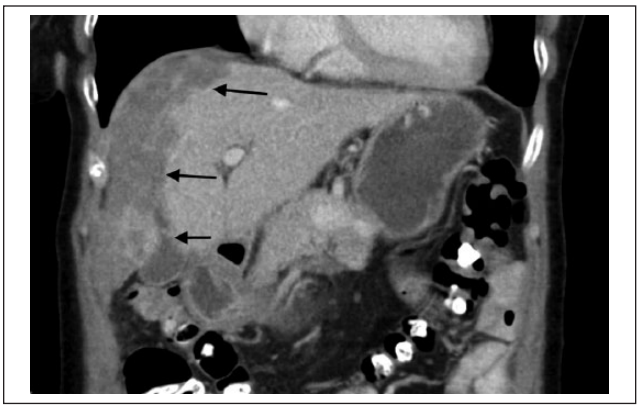

Figure 4. Computed tomography scan of December 1, 2014: Mild hepatomegaly, resolvent malignant zone.

Discussion

To our knowledge, only one earlier case report exists in the published literature[3] that describes a patient with metastatic breast cancer, who on discontinuing raloxifene experienced a reduction in global metastatic sites that continued throughout a 2-year period.

The frequency of AEWEs in breast cancer is unknown in the clinical setting. However, agonist oncological effects have been observed with raloxifene and tamoxifen in laboratory settings.[4,5] Furthermore, there have been detailed discussions regarding the proposed mechanisms of action

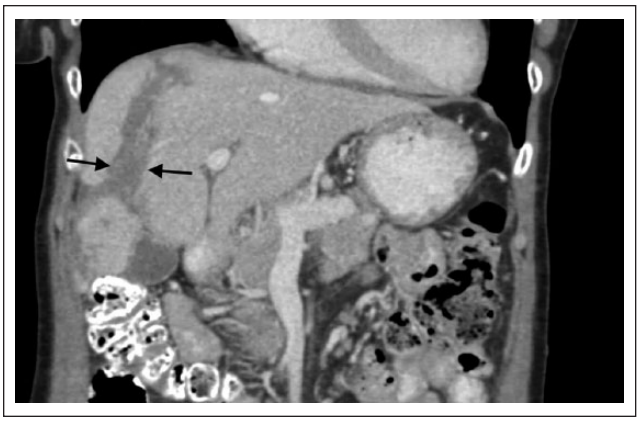

Figure 5. Computed tomography scan of April 24, 2015: Continued resolving malignancy.

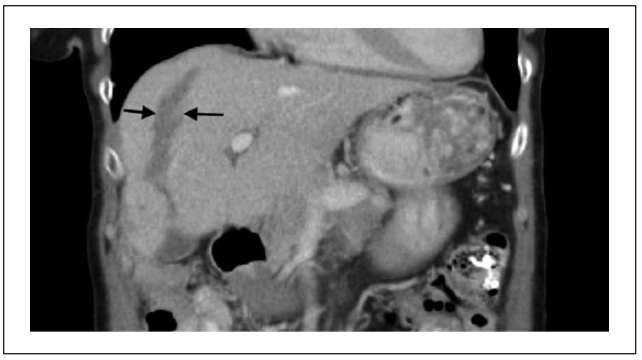

Figure 6. Computed tomography scan of October 10, 2015: Continued regression, significantly improved hepatic tissue.

regarding this area of SERM resistance and stimulated breast cancer growth.[6,7] In one model proposed by Fan and Jordan,[6] 3 phases of acquired antihormone drug resistance have been discussed where: (*a*) tumors with phase I resistance are stimulated by estrogen and SERM treatment but inhibited by aromatase inhibitors (AIs) and fulvestrant, which occurs after 1 or 2 years of therapy; (*b*) tumors with phase II resistance are stimulated by SERM treatment but are inhibited by estrogen due to apoptosis, which occurs after 5 years of therapy or as an occult disease during 5 years of adjuvant SERM therapy; and (*c*) tumors with phase III resistance potentially develop after indefinite therapy for estrogen receptor–positive breast cancer.

Because of the patient's 8-year period of using raloxifene, a phase II/III evolution of acquired drug resistance may help to explain the suspected AEWE observed in this case. The remaining physiologic estradiol/estrogens may have acted on SERM-sensitized cells and induced apoptosis on raloxifene discontinuation. Similar discussions are also being explored with acquired resistance to AIs and fulvestrant. Further mechanisms of SERM resistance may also include alterations or mutations in estrogen receptors such as estrogen receptor alpha D351Y that would convert the anti-estrogenic raloxifene–estrogen receptor complex to an estrogenic complex.[6] As a consequence, the withdrawal of raloxifene may have removed the estrogenic potential driver on breast cancer sensitive cells.

It is important to highlight that an analogous anti-androgen withdrawal effect is utilized in androgen deprivation therapy for prostate cancer.[8,9]

Our patient had been taking raloxifene for an extended period. It is uncertain at which point the potential transformation "from friend to foe" may have taken place with this patient. This medication may arguably have been inappropriate to begin with.

The use of raloxifene is not a prevalent practice in patients following a diagnosis of breast cancer.[10] Still, there could be patient populations where its anti-osteoporotic effects may be an attractive feature for its use, in particular when other anti-estrogen modulators and aromatase inhibitors are not well tolerated. In addition, raloxifene may be an experimental treatment option for recurrence risk prevention, especially in patients with a history of osteoporosis or osteopenia.

In light of this case report, some general concerns arise regarding the use of raloxifene and possibly other related agents used for chemoprevention.[11-13] It should be explored whether a subgroup of patients who experience an initial breast cancer diagnosis when using raloxifene may in fact be susceptible to an AEWE.

Furthermore, this case should serve as a reminder to health care providers that patient intuition may in fact be correct and should not be dismissed from the outset. At times careful observation may be the more appropriate course of action, versus aggressive and potentially harmful therapeutic intervention. We hope this report will add another piece of information to the rather unexplored subject area of AEWE in patients with breast cancer.

Acknowledgments

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Authors' Note

Written informed consent to publish case related data and images was provided by the patient.

Declaration of Conflicting Interests

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