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Case of Hormone-Positive Breast Cancer Recurrence after 41 Years, with Literature Review on Breast Cancer Management Evolution

***Stuti M Trivedi*[1]*; Rene R Rubin*[2]**

[1]*Government Medical College, Veer Narmad South Gujarat University, Gujarat, India.*

[2]*Director of Rittenhouse Hem/Oncology, Philadelphia, Pennsylvania.*

***Corresponding Author(s): Stuti M Trivedi**

Government Medical College, Veer Narmad South Gujarat University, Gujarat, India.

Tel: +91-8511548450; Email: stutitrivedi115@gmail.com

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Abstract

Breast cancer has the highest chances of recurring within the first five years after initial treatment. Recurrence beyond this period, known as late recurrence, which is more common in women with high lymph node involvement, large tumor size, triple-negative tumors, and estrogen receptor-positive tumors. We present a very rare case of estrogen receptor-positive breast cancer recurrence for the second time nearly four decades after the primary diagnosis. In our opinion, two unconventional approaches contributed to keeping the cancer cells dormant for four decades: bilateral hystero-salpingography and the administration of Ramoxifen for five years after completing treatment with Tamoxifen. Additionally, this article offers a literature review on the evolution of breast cancer management.

Case Report

An 89-year-old woman from Ashkenazi jewish descent had undergone right lumpectomy in August, 1983 for a stage 3 infiltrating duct carcinoma with ER/PR(Estrogen-progesterone) receptor positivity followed by prophylactic bilateral mastectomy. She was started on combination chemotherapy regimen CMFVP (Cyclophosphamide, Methotrexate, Fluorouracil, Vincristine, Prednisone)weekly for 9 months and Tamoxifen reportedly for 5 years. In 1984, she underwent Bilateral breast reconstruction and prophylactic TAH-BSO (Total abdominal hysterectomy with bilateral salpingo-oophorectomy). She was in remission until August 1990, when she had recurrence of cancer in her right chest wall. After radiation it was declared to be in remission. After many years, she was found to be osteoporotic and was treated with Raloxifene. She was on it for approximately five years.

Nearly 41 years after the initial diagnosis, in 2024, she noticed an itchy, abnormal scar on her right lateral superior chest and was advised by her dermatologist to get a punch biopsy which showed an adenocarcinoma of breast origin. PET (Positron Emission Tomography) scan was overall normal. Immunohistochemistry of the specimen showed cytokeratin 7 and pan-cytokeratin were diffusely and strongly positive and p63, TTF-1 (Thyroid Transcription Factor-1) and CEA (Carcinoembryogenic Antigen) were negative. Biomarkers showed positive Estrogen receptor with >95% strong intensity, Positive progesterone receptor with >30% strong intensity and HER2 (human epidermal growth factor 2) immunohistochemistry was equivocal for over expression (score 2+). K167 showed a low proliferative rate, 3%. The FISH (Fluorescence In Situ Hybridization) study came back negative for HER2 expression.

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With these clinical and cytological findings, she was diagnosed as ER/PR and HER-2-positive ipsilateral recurrent breast cancer more than four decades after primary treatment.

Her genetic testing revealed no BRCA or other significant mutations, and investigations found no evidence of metastasis. Thus, she was diagnosed with BRCA-negative, ER/PR-positive recurrent localized adenocarcinoma and initiated treatment with exemestane 25 mg, with ongoing periodic assessment.

Discussion

Since the mid-2000s, age-adjusted annual female breast cancer incidence has increased by approximately 1% and death rate incidence has been decreasing by approximately 1.2% [1]. We have made significant progress in the field of breast cancer management. Radical mastectomy was the predominant treatment for breast cancer in the past. However, radiotherapy changed this significantly. In the mid 20th century, post-mastectomy radiotherapy showed improved survival rates [2]. Until the 1980s, regional node irradiation was standard practice for node-positive or high-risk breast cancer [3]. This has changed now to modern techniques like partial breast irradiation, intraoperative radiotherapy, and brachytherapy. The shift from radical mastectomy to lumpectomy in the late 1900s was supported by trials such as NSABP B-06, demonstrating that lumpectomy with radiotherapy was an effective alternative to radical mastectomy [3]. Furthermore, the discovery of cytotoxic chemotherapy, combination therapies emerged as vital adjuvant treatments. Cyclical CMF (cyclophosphamide, methotrexate, fluorouracil) achieved response rate of >50% in metastatic breast cancer, prompting interest in breast-conserving surgeries [4]. The CMFVP (cyclophosphamide, vincristine sulfate, methotrexate, fluorouracil and prednisone) also known as the Cooper regimen in the 1970s further improved outcomes, encouraging modifications [5,6]. Neoadjuvant therapy, which involves initiating chemotherapy before surgery was initiated which had shown a 50% reduction in tumor size [3]. Today, a variety of tailored chemotherapy options such as AC, AC-T (doxorubicin, cyclophosphamide, paclitaxel), CAF (cyclophosphamide, doxorubicin, fluorouracil), CMF, FEC, and TAC (docetaxel, doxorubicin, cyclophosphamide) are used as neoadjuvant, primary management or as an adjuvant therapy based on individual patient needs, tumor characteristics and treatment tolerances in the comprehensive management of breast cancer.

Thomas Beatson's 1896 observations on temporary remission of breast cancer post-surgical oophorectomy highlighted ovarian secretion's role in cancer growth, inspiring anti-hormonal therapies [2]. Estrogen receptors were discovered due to observed changes in breast cancer with menstruation, leading to Tamoxifen's development and FDA approval in 1977, revolutionizing hormone therapy [2]. Tamoxifen reduces recurrence and mortality in estrogen receptor-positive breast cancer over 5 years [7], with 10-year therapy showing a 2.8% reduction in breast cancer mortality [8]. Raloxifene, used for osteoporosis, also prevents hormone receptor-positive breast cancer. The STAR trial found Raloxifene comparable to Tamoxifen in preventing invasive breast cancer in postmenopausal women [9], favoring Tamoxifen for high-risk premenopausal women and Raloxifene for postmenopausal women at risk of osteoporosis. In the mid to late 1900s, before the genetic testing era, trials showed adjuvant oophorectomy benefits alongside radiation and surgery, enhancing disease-free and overall survival. Subsequent trials showed comparable advantages of surgical or medical oophorectomy (with gonadotropin-releasing hormone agonists) to cytotoxic chemotherapies, particularly in hormone receptor-positive tumors [10]. Prophylactic hysterectomy and oophorectomy are now rare, except in specific genetic cases like BRCA positivity. Furthermore, discovery of the HER2 gene in 1987 led to Trastuzumab's approval for HER2-positive metastatic breast cancer, reducing recurrence by 50% with paclitaxel [3]. In 1994, BRCA1 and BRCA2 were identified which were associated with increased breast and ovarian cancer risks, notably in Jewish families. This marked a significant breakthrough in the genetic association of cancer. Prophylactic bilateral salpingo-oophorectomy and mastectomy are recommended for mutation carriers to prevent these cancers which is evidently beneficial [2]. It reflects the evolution of breast cancer management. With a broad array of treatment options available today, decisions are tailored based on patient characteristics, tumor type and staging, and patient preferences.

This unusual case prompted us to consider the management steps that may have kept her breast cancer dormant. Two unconventional approaches stand out. Firstly, the prophylactic TAH-BSO. This procedure eliminated cyclical hormonal fluctuations, exerting a profound impact on estrogen and progesterone-positive breast cancer. Despite not being BRCA positive, she received treatment similar to BRCA mutation carriers. Historically, such procedures were more common due to limited advanced management options but not anymore. While developed countries now prioritize chemotherapy and targeted therapies, in many developing nations, this could be a cost-effective option for recurrence prevention. As our case suggests it may offer long-term preventive benefits, potentially alleviating financial burdens associated with advanced therapies. Another unconventional step involved administering Raloxifene for nearly five years after completing Tamoxifen. While current data does not support this practice, we speculate that continuing Raloxifene after Tamoxifen may have maintained cancer cell dormancy for an extended period. It's plausible that without Raloxifene, recurrence might have occurred much sooner. This report raises the question of exploring simpler approaches such as oophorectomy and adjunctive Raloxifene for preventing hormone-positive breast cancer recurrence in high-risk women. However, further research and data are necessary to validate these strategies.

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