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CASE REPORT

# Experience with ospemifene in patients with vulvar and vaginal atrophy and a history of breast cancer: case studies

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## Abstract

Women with breast cancer are at a higher risk of developing vulvar and vaginal atrophy (VVA), a major component of the genitourinary syndrome of menopause, due to the combined estrogen-depleting effects of chemotherapy, adjuvant hormone therapy, and menopause. Ospemifene is approved to treat VVA in postmenopausal women with a history of breast cancer after completion of all breast cancer (including adjuvant) treatments. This article examines the background characteristics and outcomes in two postmenopausal women with a history of breast cancer who were treated with ospemifene for VVA. In the first case, a 78-year-old postmenopausal woman developed VVA while on aromatase inhibitor therapy for breast cancer. In the second case, a 54-year-old woman developed VVA many years after completing breast cancer therapy but not long after menopause. Both women had meaningful symptomatic improvement within 3 months of starting ospemifene treatment. Further improvement allowed each woman to resume sexual relations which had been a concern at presentation. Mammography and breast ultrasound imaging indicated no changes in breast tissue during treatment. Ospemifene is a useful therapeutic option for postmenopausal women with VVA and a history of breast cancer.

**Keywords:** breast cancer, ospemifene, vulvar and vaginal atrophy.

## Citation

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## Introduction

Vulvar and vaginal atrophy (VVA), a major component of the genitourinary syndrome of menopause, occurs in approximately 50% of postmenopausal women[1,2] as a consequence of declining estrogen levels.[3] Main symptoms of vaginal dryness, irritation, and dyspareunia can have a negative impact on sexual activity, relationships, and everyday activities.[4]

Women with breast cancer are at an increased risk of developing VVA due to the combined effects of chemotherapy, adjuvant hormone therapy, and menopause.[3,5] Most women with hormone receptor-positive breast cancer receive systemic adjuvant endocrine therapy for at least 5 years to prevent recurrence.[6,7] Tamoxifen, a selective estrogen receptor modulator (SERM), blocks the proliferative actions of estrogen on mammary epithelium.[8] Aromatase inhibitors (e.g., anastrozole, exemestane, letrozole) block estrogen production in peripheral fat.[7] Adjuvant endocrine therapy can induce or exacerbate estrogen deprivation symptoms.[7] Between 50 and 75% of breast cancer survivors develop VVA and generally experience more severe symptoms than those in the general population of postmenopausal women.[6]

The goal of treating VVA is to alleviate symptoms and reverse the atrophic changes.[9] Although estrogen therapies are a logical starting point, systemic and local estrogen therapies are contraindicated in women with a history of breast cancer.[5] In women with significant VVA, including those with a history of hormone receptor-positive breast cancer, several medical societies support the use of vaginal estrogen therapy in consultation with an oncologist when symptomatic relief with non-hormonal products is insufficient.[10] Despite this guidance, physicians are generally not comfortable prescribing vaginal estrogen therapy to women with a history of breast cancer.[10,11]

Ospemifene is an SERM approved for treatment of VVA in postmenopausal women with a history of breast cancer after completion of breast cancer (including adjuvant) treatment.[12] The tissue-specific effects of ospemifene, which include estrogen-like effects on the vaginal epithelium, an estrogenic effect on bone, neutral effects on the endometrium, and

an antiestrogenic effect on breast tissue,[13] support this indication.

Here we examine background characteristics and outcomes in two postmenopausal women with a history of breast cancer who were treated with ospemifene for VVA. As patient-specific information was deidentified to ensure anonymity, patient consent was not required.

## Case 1

Case 1 involves a 78-year-old woman with a bodyweight of 60 kg and height of 1.6 m (body mass index [BMI] 23.4 kg/m$^2$) with severe VVA and a history of breast cancer. She was nulliparous and entered menopause at 50 years of age. She had used hormone replacement therapy for 5 years prior to her breast cancer diagnosis. She was a previous smoker. She was physically active (walks 5 km every day).

In 2009, the patient self-palpated a nodule in the right breast. Mammography revealed a nodule (3 x 2 cm) with microcalcifications and a breast imaging-reporting and database system (BI-RADS) breast density score of 5 (highly suggestive of malignancy).[14] A diagnosis of ductal infiltrating breast cancer was confirmed by biopsy. Right mastectomy and lymphadenectomy were performed, followed by chemotherapy and reconstructive surgery. She experienced secondary right arm lymphedema. Aromatase inhibitor therapy was started in 2009, and continued for 5 years (until 2014).

In May 2012, during treatment with aromatase inhibitors, the patient developed severe VVA, which she managed with moisturizers and pelvic floor rehabilitation. Vaginal dryness, vulvar itching, vaginal irritation, and dyspareunia had made sexual intercourse impractical. Vaginal fluid pH was 6. Local treatment was maintained with over-the-counter moisturizers and lubricants.

In July 2018, approximately 4 years after ending aromatase inhibitor therapy, the patient presented with ongoing symptoms of VVA. She had a new partner and was enquiring about the possibility of resuming sexual intercourse. Vaginal ultrasound showed uterine and ovarian atrophy. Mammography and breast ultrasound were normal (BI-RADS score 1).

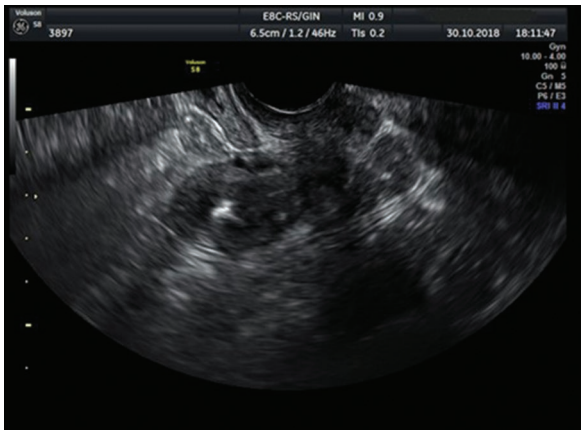
Treatment with ospemifene 60 mg daily began in July 2018. After 3 months, improvement was observed in vaginal dryness, itching, and irritation. Vaginal fluid pH was 4.5. A follow-up vaginal ultrasound showed atrophy of the uterus and ovaries (Figure 1).

By February 2019, after 7 months' treatment with ospemifene, there was further improvement in dyspareunia and the patient had resumed sexual intercourse. A mammogram showed no breast abnormalities.

## Case 2

The case describes a 54-year-old woman with a bodyweight of 62 kg and height 1.66 m (BMI 22.5 kg/m$^2$). In February

**Figure 1. Vaginal ultrasound showing atrophy of the uterus and ovaries.**




1999, a pregnancy was terminated at 14 weeks due to a large endometrial polyp. This was followed in April 1999 by hysteroscopy with polyp resection. In October 2000, a fast-growing myoma was removed having reached a size of 9 x 7 cm.

Three days prior to the myomectomy, at the age of 37 years, the patient detected a nodule in her left breast. Examination and breast sonography suggested a fibroadenoma, which was surgically removed. Pathology indicated a grade 3 infiltrating ductal carcinoma (20 x 15 mm). In November 2000, the patient underwent surgical enlargement of the lumpectomy and axillary lymphadenectomy (8 negative axillary nodes). A body extension study was negative for tumors at other sites. The tumor was classified as luminal A, T1AN0M0. Post surgery, the patient received chemotherapy and radiotherapy, followed by tamoxifen from May 2001 to October 2006.

In December 2011, a right ovarian endometrioma (6 cm) was resected.

The patient entered menopause in July 2014.

In May 2017, the patient presented with concerns about vaginal dryness and deteriorating sexual relations. Examination revealed atrophy of the external genitalia, thinning and dryness of the vagina, and vaginal bleeding on contact with the speculum. Vaginal fluid pH was 6.1. A vaginal ultrasound indicated an endometrial thickness of 2 mm and atrophy of the uterus and ovaries.

Laboratory blood values were hemoglobin 13.2 g/dL, cholesterol 235 mg/dL, triglycerides 139 mg/dL, high-density lipoprotein 64 mg/dL, low-density lipoprotein 143 mg/dL, vitamin D 37 mg/dL, thyroid stimulating hormone 1.1 mU/L, and serum carboxy-terminal collagen cross-links (a bone resorption marker) 0.44 mg/L.

Mammography and breast ultrasound were normal: The American College of Radiology (ACR) breast density was category B and the BI-RADS score was 2.[14] Bone mineral density (BMD) T-scores were +1.2 (lumbar spine) and +0.8 (total hip).

The patient reported that vaginal dryness and lack of lubrication during sexual relations were causing pain, and that her loss of interest in sexual relations was placing a strain on her relationship. In self-assessing her symptom severity over the past 4 weeks, she scored 10/10 for dyspareunia and 10/10 for vaginal dryness. Her self-rated quality of life was about 23% of 'best possible.' Prior to presenting, she had tried using local hyaluronic acid twice weekly for 6 months, but was not comfortable applying the cream and had not detected any improvement in her symptoms or sexual desire during treatment. Hormone therapy was not an option due to her breast cancer history.

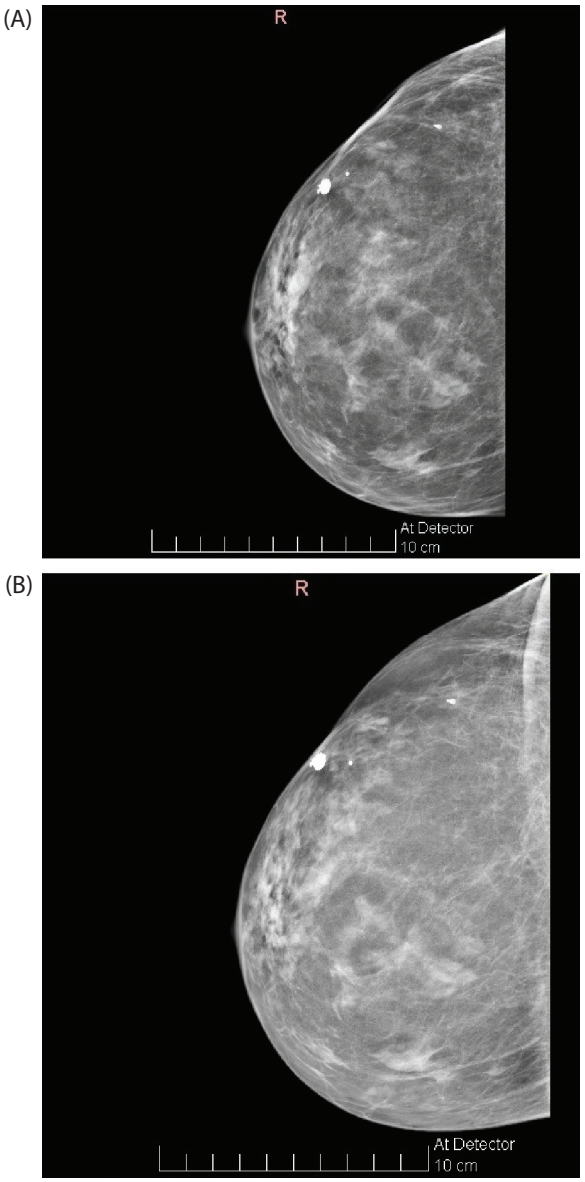
In June 2017, she began treatment with ospemifene 60 mg daily. Treatment was selected based on her preference for oral medication, her desire to recover her libido, and the pharmacological profile of ospemifene. After 3 months' treatment, she reported less vaginal dryness and a return of sexual desire. A gynecological examination showed improvement in vaginal hydration and a thicker and more elastic vaginal mucosa. Vaginal fluid pH was 4.3.

In January 2018, after 6 months' treatment with ospemifene, further improvement was observed. Symptom severity scores for dyspareunia and vaginal dryness were both 0/10, and her self-rated quality of life was about 83% of 'best possible.' Endometrial thickness on ultrasound was 2 mm.

After 15 months of ospemifene treatment, cytology indicated no vaginal atrophy. Mammography and breast ultrasound were normal (ACR breast density category B; BI-RADS score 2) (Figure 2).

Endometrial thickness was 2 mm on ultrasound. T-scores at the lumbar spine and total hip were +1.1 and +1.5, respectively. The patient asked to continue ospemifene therapy and reported that her sexual desire was similar to that before menopause.

**Figure 2. Mammography showed no increase in breast density from (A) September 2017, after 3 months' treatment with ospemifene; to (B) September 2018, after 15 month's treatment with ospemifene.**




## Clinical overview

Due to the large number of nuclear receptor regulators of estrogen receptors, estrogen receptors are differentially expressed and controlled in various tissues.[1] Ospemifene has estrogen-like activity in the vagina, bone, and cardiovascular system, neutral activity in the uterus, and an estrogen antagonistic effect in breast tissue.[15] This pharmacological profile supports use of ospemifene in postmenopausal women with VVA who have survived breast cancer.

The two cases reported here are distinguishable in that the patient in case 1, who had been postmenopausal for many years, developed VVA while on aromatase inhibitor therapy for breast cancer. Conversely, the patient in case 2 developed VVA many years after completing breast cancer therapy but only a few years after menopause onset. The preservation of ovarian function and development of an ovarian endometrioma after chemotherapy observed in this case are highly unusual. In both women, the most troublesome symptoms of VVA improved within 3 months of starting ospemifene. By about 6 months, vaginal alkalinization was normalized, and both women were able to resume sexual relations. There was no evidence of breast tissue changes during treatment. In case 2, ospemifene had neutral effects on the endometrium and BMD. The decision to prescribe ospemifene for the patient in case 1 is notable give the association between advanced age and thrombosis risk.[16] In the ospemifene clinical trials program, no increased risk of venous thromboembolism was observed although 95% confidence limits were wide.[17] Despite the patient's age (78 years), her normal BMI and high level of physical activity also afforded protection against venous thromboembolism.

Preclinical studies demonstrated that ospemifene has an estrogen antagonist effect on breast cancer in preventive and

**Table 1. Mammogram and breast palpation findings during treatment with ospemifene.**

| Examination | Finding | Ospemifene 60 mg/day | | | Placebo | | |
|---|---|---|---|---|---|---|---|
| Mammography | | Baseline (n=362) | 12 months (n=269) | Change | Baseline (n=63) | 12 months (n=47) | Change |
| | Normal | 88.1% | 92.2% | ↑ | 93.7% | 91.5% | ↑ |
| | Abnormal, NCS | 11.9% | 7.8% | ↓ | 6.3% | 8.5% | ↓ |
| Breast palpation | | Baseline (n=1100) | 12 months (n=354) | Change | Baseline (n=821) | 12 months (n=90) | Change |
| | Normal | 97.2% | 99.2% | ↑ | 97.7% | 100% | ↑ |
| | Abnormal, NCS | 2.8% | 0.8% | ↓ | 2.3% | 0% | ↓ |

Compiled using data from Simon et al. (2018).[21]
NCS, not clinically significant.

treatment settings.[3] In mouse models, ospemifene was shown to inhibit the growth of premalignant mammary lesions and slow the progression to invasive carcinoma.[18,19] Clinical data with ospemifene support a neutral effect in breast tissue. In a 52-week trial of ospemifene 60 mg daily (n=363) *versus* placebo (n=63) in postmenopausal women with VVA, there were no reports of breast cancer or breast-related adverse events.[20] In a *post-hoc* analysis of 1242 women with moderate-to-severe dyspareunia who received ospemifene 60 mg daily (median duration of therapy 86 days) across six phase II or III clinical trials, the incidence of breast cancer or other breast-related treatment-emergent adverse events was 2.5 *versus* 2.2% for placebo (n=958).[21] In the subgroup treated with ospemifene for 12 months, no clinically significant abnormalities were observed on mammography or by breast palpation (Table 1).[21] Another *post hoc* analysis of phase III clinical trials of ospemifene 60 mg daily in women with VVA found a similar clinical efficacy and adverse events profile in women with (n=11) and without (n=1091) a history of breast cancer.[22]

More recently, a review was conducted of the United States ISB MarketScan Commercial and Medicare Supplemental Insurance Claim database, from 2013 to 2017, to investigate the incidence of breast cancer in women with VVA and no prior evidence of breast cancer who had received ospemifene (n=2528) or were untreated (n=118,623).[23] The mean duration of ospemifene treatment was 272 days, and average follow-up was 803 days. After matching data for age, index date (year), Charlson Comorbidity Index score, geographic region, and follow-up duration, the incidence of breast cancer was 0.9/1000 person-years with ospemifene and 1.6/1000 person-years with no treatment. The incidence in the untreated group was similar to that for invasive breast cancer estimated by the US Surveillance, Epidemiology and End Results program for the period 2010–2014, which ranged from 1.9/1000 person-years in women aged 45–49 years to 4.5/1000 person-years in women aged 70–74 years.

## Conclusion

Patients with breast cancer who receive adjuvant endocrine therapy have an increased risk of developing VVA. Treatment choices in these women are limited because of concerns about the use of local estrogens. The women in these case studies with a history of breast cancer achieved relevant improvement in VVA symptoms within 3 months of starting ospemifene treatment, and no mammographic changes were observed during continued treatment. Ospemifene may be a useful therapeutic option for postmenopausal women with VVA who are not candidates for local vaginal estrogen therapy, including women with a history of breast cancer, after breast cancer treatment (including adjuvant therapy) has been completed.

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