Clinical Vignettes

Lichen Sclerosus in a Breast Cancer Survivor on an Aromatase Inhibitor: A Case Report

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Lichen sclerosus is a commonly misdiagnosed disease that is characterized by thinned, hypopigmented, crinkled skin that often forms a figure-eight shape around the vaginal and anal openings. We present a case of advanced lichen sclerosus in a 53-year-old female patient prescribed a nonsteroidal aromatase inhibitor after the excision of a breast cancer tumor. We present a diagnostic approach to lichen sclerosus by recognizing its common figure-eight pattern, and we review the known causes and treatment of lichen sclerosus. Research has shown that lichen sclerosus is more common in low estrogen states, and thus it is logical that aromatase inhibitors could increase a patient's risk for developing this disease. We therefore propose that all patients prescribed aromatase inhibitors undergo regular vulvo-vaginal exams to rule out lichen sclerosus and other hypoestrogen-related vulvo-vaginal problems.

malignancy,¹ underscoring the importance of diagnosis and surveillance.

We present a case of advanced lichen sclerosus in a patient prescribed a nonsteroidal aromatase inhibitor after primary breast cancer treatment. Given the expanding role of primary care clinicians in cancer survivorship, the ability to recognize and appropriately treat vulvar conditions that arise in breast cancer survivors is critically important. The need for regular vulvo-vaginal inspection must be highlighted, given recent widening of the recommended interval between Pap tests to up to five years for women aged 30–65.² Many of the changes associated with long-term, untreated lichen sclerosus are irreversible; therefore, detection and treatment during the asymptomatic stage is crucial. Table 1 summarizes the disease's key points.

KEY WORDS: lichen sclerosus; aromatase inhibitor; complication; cancer survivorship; atrophic vulvovaginitis.

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INTRODUCTION

Lichen sclerosus is a commonly misdiagnosed disease that generally affects perineal skin. Patients often present with vulvar itching and/or burning. Lesions may present as small light spots that coalesce into larger patches; the skin becomes thin, crinkled, and susceptible to bruising and tearing. The classic presentation manifests in a figure-eight pattern extending from clitoral hood to anus; however, lichen sclerosus can include a wide range of abnormal vulvar lesions. Untreated, lichen sclerosus can lead to intensive scarring, ulceration, labial fusion, and labial/clitoral resorption; these changes greatly impact quality of life. Additionally, vulvar lichen sclerosus is associated with squamous cell carcinoma with up to a 5 % incidence of

CASE REPORT

A 53-year-old lesbian presented for evaluation of progressively worsening vulvo-vaginal discomfort and sexual difficulties since beginning anastrozole 3.5 years earlier. A stage 1, 1.2 cm, grade 3 infiltrating ductal carcinoma of the right breast was diagnosed eight years prior to evaluation. She was treated with wide excision; the tumor was estrogen receptor (ER) positive, two sampled sentinel lymph nodes were tumor-free, and no lymphovascular invasion was seen. She received four cycles of doxorubicin and cyclophosphamide, then radiation therapy, completed 3.5 years of tamoxifen, and subsequently was switched to anastrozole. She last menstruated during chemotherapy; after menopause ensued, she noted vaginal dryness, initially ameliorated by using lubricants during sexual activity. She was offered but declined to use vaginal estrogens because of her tumor's ER positive status. Medical history was otherwise notable for borderline osteopenia, vitamin D deficiency, and infrequent lower tract urinary infections. Medications on presentation (in addition to anastrozole) included: aspirin 81 mg QD, vitamin D 3000 IU and calcium citrate 600 mg daily, and post-coital nitrofurantoin as needed.

Complaints upon presentation included intermittent 6–7/10 burning involving the entire vulva, loss of pleasurable sensations during sexual stimulation of the external genitalia.

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Table 1. Lichen Sclerosus: Key Points of the Disease and Its Treatment

Key Points:	
• Women taking medications that induce an exaggerated hypoestrogen state (such as anastrozole) may be at an increased risk for developing lichen sclerosus.	
• Women taking aromatase inhibitors should receive annual surveillance vulvo-vaginal exams regardless of the need for cervical cancer screening.	
• Perineal lichen sclerosus is characterized by thinned, hypopigmented, crinkled skin that often forms a figure-eight shape around vaginal and anal openings.	
• The treatment of choice is a high-potency, topical corticosteroid, such as clobetasol propionate.	
• Clinicians should maintain a high index of suspicion for malignant transformation and biopsy should be performed when lesions are atypical, persistent, or recurrent.	

lia, and extreme discomfort during any kind of vaginal penetration. Pap and sexually transmitted infection (STI) testing were consistently negative. The patient believed she “tore tissue” during her last pelvic exam with a gynecologist six months earlier, because she experienced searing pain during the procedure and spotted for several days afterwards. At the time of examination, the gynecologist did not diagnose any disease. The patient delayed seeking another examination. She recounted a loving relationship with her partner, though they were infrequently sexually active due to the aforementioned symptoms. She denied vaginal discharge, fever, and pelvic or back pain. She endorsed occasional burning when urine touched vulvar skin, but had not recently noted urinary frequency, urgency, hematuria, foul smelling or cloudy urine.

On physical examination, she appeared well, with normal vital signs and a body mass index of 19.5. Pelvic exam revealed a normal mons pubis. The labia majora were atrophied; the labia minora were partially fused across the urethral and vaginal orifices and the tissue was pulled taut, thinner than normal, and demonstrated patchy, pearly-white, cicatricial scarring. The scarring appeared in a figure-eight pattern, blooming out around the vaginal and anal openings. A vaginal examination done cautiously using a pediatric speculum revealed thinning of the vaginal epithelium, loss of rugae, and a pale, dry appearance. No appreciable vaginal discharge was detected. A single finger digital examination revealed decreased elasticity and distensibility of the vaginal vault; no masses or tenderness were appreciated.

As a result of the figure-eight pattern of scarring and labial fusion, as well as the patient's estrogen-suppressed state, a preliminary diagnosis of lichen sclerosus was made. Urinalysis revealed SG 1.010, pH 6.0, negative nitrite, leukocyte esterase, protein, glucose, ketones, bilirubin, 1 RBC, and 0 WBC. A biopsy confirmed: “Lichen sclerosus et atrophicus. No fungi seen on PAS-reacted sections.”

The primary treatment was clobetasol propionate 0.05 % ointment, applied to affected areas twice daily for two weeks, then nightly for two months, then twice weekly for

long-term maintenance. Additionally, she used low dose vaginal estrogen in the form of 10 mcg estradiol vaginal tablets, inserted twice weekly to reduce local hypoestrogen effects. She was offered surgical intervention to release labial fusion, but declined. After consultation with dermatology and oncology, she opted to continue anastrozole at the same dosage, as there are no data to support regression of lichenification following discontinuation.

The patient no longer experiences vulvar pruritus or dysuria. She remains infrequently sexually active; speculum vaginal examination remains challenging due to atrophic changes. Her genitalia continue to demonstrate chronic, pearly-white, atrophic changes and a narrow vaginal introitus, as the scarring and loss of vulvar architecture due to lichen sclerosus are permanent. However, there has been no evidence of acute or persistent inflammatory changes or erosions to merit re-biopsy to exclude neoplastic transformation.

DISCUSSION

The differential diagnosis of vulvar pruritus and pain includes contact dermatitis, atrophic vulvovaginitis, lichen sclerosus, lichen planus, and vulvar intraepithelial neoplasia. These conditions are frequently misdiagnosed by providers and incorrectly self-treated by patients; therefore, careful examination, close observation during initial therapy, and ongoing surveillance are warranted to assure accurate diagnosis and appropriate treatment.

Particular care is needed to avoid attributing all vulvar symptoms in postmenopausal women to atrophic vulvovaginitis. Atrophic vulvovaginitis is an inflammation of the vulva/vagina as a result of decreased lubrication, with fragility and loss of tissue elasticity. Patients with atrophic vulvovaginitis often present with complaints of dryness, itching, burning, and pain. Atrophic vulvovaginitis is caused by low estrogen levels and prevalence approximates 50 % in postmenopausal women.³ Treatment with low-dose, topical estrogen restores tissue integrity and is highly effective in relieving symptoms.⁴ Concomitant administration of a progestogen is generally not indicated during administration of topical, low-dose estrogen, although evidence supporting long-term endometrial safety is lacking. Because endometrial hyperplasia increases with increasing dose and duration of estrogen exposure, prompt evaluation of uterine bleeding occurring in this context is warranted.⁵

There has been little research on the safety of low-dose vaginal estrogen in women with estrogen-sensitive tumors. In one study, 69 of 1,472 breast cancer survivors (36 % were estrogen receptor positive (ER+); 48 % were on tamoxifen) received low-dose vaginal estrogen for one year and were followed for 5.5 years. No increase in breast cancer recurrence was observed among those receiving estrogen.⁶ In another small study of ER+breast cancer

survivors ($N=7$) taking aromatase inhibitors, serum estradiol levels were monitored during initiation of low-dose vaginal estrogen. A short-term rise in serum estradiol was observed, reversing the estrogen suppression achieved via aromatase inhibition.⁷ Until more research is conducted, clinicians and patients must make individualized decisions whether or not to use low-dose vaginal estrogen by considering recurrence risk and quality of life.

Patients with lichen sclerosis may present with complaints similar to those with atrophic vulvovaginitis, most commonly, itching, burning and pain. Lichen sclerosis is a T-cell mediated skin disorder that can involve a small area, or may extend to include the entire vulva and perianal region. It is characterized by thinned, hypopigmented, crinkled skin that often forms a figure-eight shape around the vaginal and anal openings (Fig. 1).

Patients may also exhibit fusion of the labia minora, phimosis of the clitoral hood, purpura and fissures. The figure-eight shape of lichen sclerosis is a helpful diagnostic indicator, but may not be present. Symptoms of lichen sclerosis do not improve significantly with low dose vulvo-vaginal estrogen alone.

The causes of lichen sclerosis are not well understood. Research suggests that lichen sclerosis may be related to autoimmunity,⁸ genetic susceptibility, hormonal influences, and infectious agents such as human papillomavirus and hepatitis C.¹ One recent study found an association between lichen sclerosis and diabetes mellitus and previous pelvic

surgery.⁹ More research is needed to determine the role of these factors.

Menopause-related vulvo-vaginal atrophy is strongly associated with use of aromatase inhibitors in treatment of estrogen-dependent breast cancer.¹⁰ Lichen sclerosis is also more common in low estrogen states;¹ thus, it is logical that aromatase inhibitors could also increase the risk for developing this disease. We propose that all patients prescribed aromatase inhibitors undergo annual vulvo-vaginal exams to rule out lichen sclerosis and other hypoestrogen-related vulvo-vaginal problems, beginning within one year of starting anastrozole. Given the widening recommended interval between cervical cancer screening tests, these exams should occur on a routine basis, regardless of whether or not a complete pelvic exam is required for other reasons.

There is little known about lichen sclerosis in the setting of anastrozole; we therefore share what is known about lichen sclerosis treatment generally. The most commonly accepted treatment option is described in this case—a regimen of a topical corticosteroid.¹¹ A range of potent topical corticosteroids have been studied for their efficacy in treating lichen sclerosis; the most studied is clobetasol propionate. No one formulation has proven more effective than another and more research is needed.¹ Generally, a short-term burst of high potency topical corticosteroid is followed by a less potent dosage for long-term maintenance. There are risks associated with topical steroid use, including contact sensitization, skin changes, and secondary infection.¹² Currently, evidence is lacking to document safety with long-term use. Therefore, patients using topical corticosteroids for maintenance of remission must return for regular surveillance.

Studies suggest that topical vaginal estrogens, androgens, and progesterone are not efficacious in treating lichen sclerosis.¹¹ Topical immunomodulators (tacrolimus, pimecrolimus, cyclosporine) show promise, but are generally considered second-line treatments for patients unresponsive to other options.¹² In one study, the use of tacrolimus in six patients yielded complete resolution of symptoms, with remission for up to one year with no observed adverse effects.¹³ In another study, pimecrolimus produced similar improvements in relieving pruritus and improving burning/pain as clobetasol propionate. However, pimecrolimus was less effective with regard to global degree of improvement.¹⁴ More research is needed on the effectiveness of immunomodulators.¹²

Routine biopsy is not necessary to diagnose lichen sclerosis if lesions are classic in appearance and resolve rapidly using topical corticosteroids. However, the classic figure-eight appearance is infrequent, and it is always acceptable to biopsy any lesion on the vulva to rule out cancer and confirm histologic diagnosis. Vulvar biopsy is well tolerated and it may take months for lichen sclerosis to respond to corticosteroids. As there is an association between vulvar lichen sclerosis and squamous cell or verrucous carcinoma with up to a 5 % incidence of malignancy,¹ clinicians should maintain a high index of suspicion, and biopsy should always be performed in

Figure 1. Lichen sclerosis, image courtesy of Lynn Margesson, MD.

cases associated with chronic and persistent inflammation or when atypical features are present, such as lesions that are hyperpigmented, exophytic, or demonstrate changes in vascular patterns.¹²

If the diagnosis of lichen sclerosus is confirmed by biopsy and response to topical corticosteroids remains inadequate, referral to a dermatologist or gynecologist is suggested. A specialist may evaluate the patient for intralesional steroid injection¹⁵ or photodynamic therapy,¹⁶ both of which have shown promise in small studies. In rare, advanced cases of lichen sclerosus, surgical intervention may be indicated. Once labial fusion progresses, it will not be corrected by topical corticosteroids and sharp dissection of labial adhesions may be required.¹

There is a need for ongoing surveillance, due to the risk of malignant transformation¹⁷ and a lack of research on the safety of long-term topical corticosteroid use. The American College of Obstetricians and Gynecologists (ACOG) recommends that patients return for follow-up 3 and 6 months following initial therapy. Patients with well-controlled lichen sclerosus should return for annual examinations indefinitely. Patients should also be counseled to return if new lesions appear.¹² At that time, clinicians may determine appropriate adjustments to the treatment regimen and may biopsy persistent, recurrent, or atypical lesions.

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REFERENCES

1. **Smith YR, Haefner HK.** Vulvar lichen sclerosus: pathophysiology and treatment. *Am J Clin Dermatol.* 2004;5:105–25.
2. United States Preventive Services Task Force. Screening for cervical cancer: United States Preventive Services Task Force Recommendation Statement. March 2012.
3. **Mac Bride MB, Rhodes DJ, Shuster LT.** Vulvovaginal atrophy. *Mayo Clin Proc.* 2010;85(1):87–94.
4. **Suckling J, Lethaby A, Kennedy R.** Local oestrogen for vaginal atrophy in postmenopausal women. *Cochrane Database Syst Rev.* 2006;4:CD001500.
5. **Crandall C.** Vaginal estrogen preparations: a review of safety and efficacy for vaginal atrophy. *J Womens Health (Larchmt).* 2002;11:857–877.
6. **Dew JE, Wren BG, Eden JA.** A cohort study of topical vaginal estrogen therapy in women previously treated for breast cancer. *Climacteric.* 2003;6:45–52.
7. **Kendall A, Dowsett M, Folkard E, Smith I.** Caution: vaginal estradiol appears to be contraindicated in postmenopausal women on adjuvant aromatase inhibitors. *Ann Oncol.* 2006;17:584–7.
8. **Terlouw A, Santegoets LA, van der Meijden WI, et al.** An autoimmune phenotype in vulvar lichen sclerosus and lichen planus: A Th1 response and high levels of microRNA-155. *J Invest Dermatol.* 2011 Nov 24. doi:10.1038/jid.2011.369. [Epub ahead of print]
9. **Higgins CA, Cruickshank ME.** A population-based case-control study of aetiological factors associated with vulval lichen sclerosus. *J Obstet Gynaecol.* 2012;32(3):271–5.
10. **Cella D, Fallowfield L, Barker P, Cuzick J, Locker G, Howell A.** Quality of life of postmenopausal women in the ATAC trial after completion of 5 years' adjuvant treatment for early breast cancer. *Breast Cancer Res Treat.* 2006;100(3):273–284.
11. **Chi CC, Kirtschig G, Baldo M, et al.** Topical interventions for genital lichen sclerosus. *Cochrane Database Syst Rev.* 2011;12:CD008240.
12. American College of Obstetricians and Gynecologists (ACOG). Diagnosis and management of vulvar skin disorders. *ACOG Prac Bul No 93.* 2008 May;111(5):1243–1253.
13. **Böhm M, Frieling U, Luger TA, Bonsmann G.** Successful treatment of anogenital lichen sclerosus with topical tacrolimus. *Arch Dermatol.* 2003;139(7):922–4.
14. **Goldstein AT, Creasey A, Pfau R, Phillips D, Burrows LJ.** A double-blind, randomized controlled trial of clobetasol versus pimecrolimus in patients with vulvar lichen sclerosus. *J Am Acad Dermatol.* 2011;64(6):e99–e104.
15. **Mazdisnian F, Degregorio F, Mazdisnian F, et al.** Intralesional injection of triamcinolone in the treatment of lichen sclerosus. *J Reprod Med.* 1999;44:332–4.
16. **Olejek A, Steplewska K, Gabriel A, et al.** Efficacy of photodynamic therapy in vulvar lichen sclerosus treatment based on immunohistochemical analysis of CD34, CD44, myelin basic protein, and Ki67 antibodies. *Int J Gynecol Cancer.* 2010;20(5):879–87.
17. **Gutiérrez-Pascual M, Vicente-Martín FJ, López-Esteban JL.** Lichen sclerosus and squamous cell carcinoma. *Actas Dermosifiliogr.* 2012;103(1):21–8. Epub 2012 Mar 24.