Vascular and Connective Tissue Histopathologic Alterations of the Female Lower Genital Tract in Scleroderma

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ABSTRACT. ***Objective.*** It has been suggested that women with scleroderma (systemic sclerosis, SSc) have cervical changes that may lead to obstetrical or postoperative complications. We evaluate histopathologic features characteristic of SSc in cervicovaginal tissue from women with SSc and compare them to age matched controls.

Methods. Records from the Scleroderma Registry at Wayne State University were matched with surgical specimens in the anatomic pathology files at Hutzel Hospital. Five women with SSc (2 with limited SSc, 3 with diffuse SSc; mean age 49 yrs) were identified who had cervical or vaginal tissue specimens available for evaluation. Small arterioles and surrounding connective tissue in these specimens and those from 26 age matched controls (15 normotensive, 11 hypertensive) were evaluated in blinded fashion.

Results. The following specific histopathological features were evaluated in the SSc patients: duplication or disruption of the internal elastica in 5 (100%), medial hypertrophy in 5 (100%), adventitial changes in 3 (60%), connective tissue fibrosis in 1 (20%), and vasculitis in 1 (20%). There was no significant difference in the frequency of the histopathologic changes between SSc and control patients when evaluated independently. However, the presence of 3 or more features was significantly more frequent in the SSc patients (100%) than in the controls (38%) ($p = 0.018$).

Conclusion. The histopathological features evaluated were collectively more frequent in SSc patients; however, many of the control patients also exhibited similar abnormalities. In the female lower genital tract these changes, previously attributed solely to SSc, may be related to other factors. (J Rheumatol 2002;29:1384–7)

Key Indexing Terms:
SCLERODERMA
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Scleroderma (systemic sclerosis, SSc) is an uncommon multisystem disorder that primarily affects women, and is of unknown etiology[1-4]. Histopathologically, the disease is characterized by connective tissue fibrosis and diffuse vasculopathy that can affect both the skin and visceral organs. Early alterations include adventitial changes characterized by mild perivascular and periadnexal edema and inflammation. With progression, vessel walls become thick and hyalinized, and their lumens narrowed. Although large vessels can be affected, smaller precapillary arterioles are more typically involved[5]. These microvascular alterations have also been observed in clinically uninvolved skin[6]. Although described in numerous organs, SSc involving the female genital tract has not been well documented[7-10].

MATERIALS AND METHODS

Patients. Records from 467 women in the Scleroderma Registry at Wayne State University were matched with surgical specimens in the anatomic pathology files at Hutzel Hospital. The files of the Scleroderma Registry were reviewed for pertinent clinical information. Cervicovaginal specimens from 5 women with SSc were identified and compared to 26 age matched controls that included 11 hypertensive and 15 normotensive women. Controls were selected by matching SSc patients with the most recent female patients of the same age who had cervical or vaginal tissue specimens submitted to surgical pathology for evaluation. Because 2 women with SSc (one with limited SSc and one diffuse disease) were hypertensive and the possible contribution of a hypertensive vasculopathy was unknown, both hypertensive and normotensive controls were utilized. Patients with malignancies were excluded.

Histopathological examination. Representative sections were stained with hematoxylin and eosin, trichrome, and elastic stains. Two pathologists, unaware of the diagnoses, together at a multi-headed microscope, evaluated the following histologic features to arrive at a consensus opinion: collagen deposition and connective tissue fibrosis, vasculitis, duplication or disruption of the internal elastica, medial hypertrophy, intimal proliferation, and adventitial changes (perivascular edema and inflammation).

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Analysis. Statistical analysis utilized chi-square analysis and Student t test for independent samples.

RESULTS

The clinical features of each woman with SSc from which material was evaluated are listed in Table 1, and correlated with the histopathologic findings. The average age of the 5 women with SSc was 49 years (range 40–58), and the average duration of symptoms, defined as the onset of Raynaud's, was 6 years (range 3–10). Three of the 5 women had diffuse SSc and 2 had limited SSc. All SSc patients satisfied the classification criteria for SSc of the American College of Rheumatology[11]. All the women tested positive for antinuclear antibodies (ANA). Four of the 5 women were negative for Scl-70, and the Scl-70 status of one patient (Patient 2) was unknown. No woman with SSc had evidence of systemic vasculitis. All patients with diffuse SSc had evidence of dermal vasculopathy or vasculitis manifested by digital or extremity ulcers, and had been on several different treatment regimens (Table 1) over the course of their disease. No woman with limited SSc had received immunosuppresive therapy. The preoperative diagnoses included uterine leiomyomas (2 cases), vaginal or uterine prolapse (2), and an abnormal Papanicolaou smear (1). The final pathology specimens confirmed the preoperative diagnoses in all the cases. The cervical cone biopsy, obtained for a preoperative diagnosis of an abnormal Papanicolaou smear, showed only chronic cervicitis with no evidence of a squamous dysplasia or carcinoma.

The cases exhibiting vascular or connective tissue alterations are listed in Table 2. The ectocervical squamous mucosa and the amount and distribution of endocervical glands were normal. There was no significant difference in any of the evaluated histologic features between the normotensive and hypertensive controls. Neither stromal fibrosis nor vasculitis was prominent in any of the specimens. With the exception of adventitial changes, there was no significant difference in any other single feature evaluated independently between the SSc and control groups. Adventitial changes were observed in 60% (3 cases) of SSc cases compared to 7% (1 case) of normotensive controls ($p = 0.032$), but were not statistically more frequent when

Table 1. Women with SSc: clinical history and histologic findings in cervicovaginal specimens.

	Clinical History							
Patient	Age(yrs) Gravida Para	Type of SSc	Scl 70	Raynaud's Duration (yrs)	Rodnan Skin Score**	Clincal Organ System Involvement	Various Treatment Regimens	Procedure Indication
1	43 G2P2	Diffuse	Neg	8	7***	Renal, cardiac, GI, pulmonary and pulmonary vascular, digital ulcers, HTN	D-Penicillamine, methotrexate, cyclophosphamide, prednisone	TAH/BSO, leiomyomas
2	40 G1P1	Diffuse	Not known	3 *	24	Pulmonary, GI, dermal vasculopathy	Vasodilator therapy	Cervical cone, Abnormal Pap
3	48 G1P1	Diffuse	Neg	4	13	Pulmonary, GI, dermal vasculitis with ulcers	D-Penicillamine, hydroxychloroquine-sulfate, cyclophosphamide, azathioprine	TVH, uterine prolapse
4	58 G3P3	Limited	Neg	10	3	Mild GI, HTN	None	A&P repair, enterocele
5	57 G2P2	Limited	Neg	4	2	Mild pulmonary and GI	D-Penicillamine	TVH/BSO, leiomyomas

	Histologic Findings					
	Fibrosis	Vasculitis	Duplication of Elastica	Medial Hypertrophy†	Intimal Proliferation†	Adventitial Changes
1	Absent	Present	Present	Moderate	Moderate	Present
2	Absent	Absent	Present	Mild to moderate	Mild	Absent
3	Absent	Absent	Present	Marked	Mild	Absent
4	Present	Absent	Present	Moderate	Mild	Present
5	Absent	Absent	Present	Marked	None	Present

HTN: hypertension; TAH/BSO: total abdominal hysterectomy and bilateral salpingo-oophorectomy; TVH: total vaginal hysterectomy; A&P repair: anterior and posterior repair. * Duration since diagnosis of scleroderma. ** The maximum modified Rodnan skin score is 51. *** The pretreatment Rodnan skin score is unknown. This score represents a post-treatment evaluation, and it eventually decreased to 3.

† The extent of medial hypertrophy and intimal proliferation was graded as none, mild, moderate, or severe. For statistical analysis, mild or greater alterations were considered positive in both the SSc and control groups.

Table 2. Histologic findings in cervicovaginal specimens from women with SSc compared to controls.

	Fibrosis	Vasculitis	Duplication of Elastica	Medial Hypertrophy	Intimal Proliferation	Adventitial Changes	≥ 3 Abnormal Features
Scleroderma, n = 5	1 (20)*	1 (20)	5 (100)	5 (100)	4 (80)	3 (60)†	5 (100)‡**
Hypertensive controls, n = 11	1 (9)	1 (9)	8 (73)	10 (91)	4 (36)	4 (36)	5 (45)
Normotensive controls, n = 15	0 (0)	2 (13)	14 (93)	10 (67)	6 (40)	1 (7)†	5 (33)‡
Total controls, n = 26	1 (4)	3 (12)	22 (85)	20 (77)	10 (38)	5 (19)	10 (38)**

* Number % that exhibit the feature: † p = 0.032 (adventitial changes in SSc vs normotensive controls; ‡ p = 0.033 (≥ 3 abnormal features in SSc vs normotensive controls); ** p = 0.018 (≥ 3 abnormal features in SSc vs total combined controls).

compared to the hypertensive control group (4 cases, 36%) (p = 0.60). Two of the 3 SSc cases with adventitial changes also had hypertension.

All 5 (100%) SSc patients exhibited 3 or more abnormal features compared to 10 of 26 (38%) controls (p = 0.018). A significant difference was also observed between SSc cases with greater than 3 abnormal features (100%) and normotensive controls (5 cases, 33%) (p = 0.033), but not with hypertensive controls (5 cases, 45%) (p = 0.093). The mean number of abnormalities observed in the SSc cases was 3.80 ± 1.10 compared to 2.31 ± 1.05 in the normotensive and hypertensive control groups combined (p = 0.007).

DISCUSSION

Gynecologic and obstetrical complications have rarely been reported in SSc[7-10]. One questionnaire survey of sexual function described complaints of dyspareunia related to "vaginal mucosal problems" as more common in SSc, but lacked histologic confirmation[10]. Another autopsy based series that examined 58 cases and utilized matched controls did not include genital tract organs[12].

Only a few case reports in the recent English literature have described SSc involving the cervix[7-9]. Eno, *et al* reported a "stiff" incompletely dilated cervix in a woman with SSc who experienced protracted labor[8]. Bellucci, *et al* described another 27-year-old woman, gravida 5, para 0, with SSc who underwent a cesarean section at term for failure to progress in labor[7]. A biopsy of the lower uterine segment, obtained at cesarean section, showed bands of collagen between smooth muscle fibers, and a cervical biopsy exhibited arteriolar intimal thickening. These changes were attributed to SSc and were felt to be the cause of the dystocia. Finally, Stenchever and Ng reported a 53-year-old woman, gravida 1, para 0, with rapidly progressive SSc and postmenopausal bleeding[9]. Her vulva and vagina were normal, but the cervix was described as "stoney hard." Cervical biopsies revealed a lack of endocervical glands, dense collagen bundles, arterial medial hypertrophy, arteriolar intimal proliferation, irregularly dilated surface capillaries, and a moderate lymphocytic infiltrate. Bleeding in the absence of a documented coagulopathy complicated her postoperative course. These investigators further evaluated the clinical records from 56 women with SSc as well as 9 autopsy cases, and found no further evidence of SSc involving the female genital tract.

We found that cervicovaginal vascular and connective tissue abnormalities typical of SSc were collectively more frequent in SSc compared to controls. However, many of the individual features evaluated were also observed in both control groups. With the exception of adventitial changes, we were unable to identify any single abnormality that was statistically different between the 3 groups. Overlap of histologic features with other pathologic and physiologic vascular alterations may explain our findings. Vascular changes associated with aging include many features similar to those observed in our study[13]. In kidney and lung, the changes seen in SSc may resemble those seen in malignant hypertension[5] or primary pulmonary hypertension[14], respectively. The presence of hypertension in some of the SSc patients in this study may have contributed to the alterations observed. Further, the current study is small, and larger series are needed to confirm our findings.

Although collectively more frequent in SSc, vascular alterations in the cervix and vagina previously attributed solely to SSc may be related in part to factors other than direct involvement by the disease.

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