

**TITLE**

**Development of systemic sclerosis in transgender females: a case series and review of the literature.**

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**Short running title: Systemic sclerosis in transgender females**

## **ABSTRACT**

**Objective:** Systemic sclerosis (SSc) is chronic, autoimmune connective tissue disease with a female predominance. The reason for the female predilection in SSc may relate to the difference in hormones between the genders. There are no current data on the influence male-to-female sex transition may have in the development of SSc. We report three patients who developed SSc after initiating the transgender process, and review current literature in regards to transgender patients with connective tissue disease (CTD).

**Methods:** We describe the clinical features and disease course of three transgender patients who developed SSc after their transition from male-to-female, who presented to our centre. Two additional transgender cases described in the literature with CTD were included in this review.

**Results:** All three patients developed SSc after having started the hormonal therapy required to transition. Two patients had surgical procedures preceding their diagnosis of SSc. Antibody profile, time of onset and disease features differed among our patients. Hormonal therapies were continued in all patients and they received the standard therapy for SSc. One patient died from complications of their disease. Only two cases describing the development of CTD in transgender patients were identified in the literature and both of these patients were diagnosed with systemic lupus erythematosus (SLE).

**Conclusion:** This case series suggests that the hormonal modification as part of gender transition may be relevant in development of SSc. No further conclusions can be drawn on the continuation or not of HT.

**Key words:** scleroderma, systemic sclerosis, hormones, transgender, connective tissue diseases

## **Introduction**

Systemic sclerosis (SSc) is a female predominant, autoimmune connective tissue disease. It is characterized by vasculopathy, inflammation with autoantibody production, and excessive collagen deposition in the skin and internal organs, leading to fibrotic changes <sup>1</sup>. The female to male ratio observed in several SSc cohorts ranges from 5:1 to 12:1 <sup>2</sup>. The reason for this increased female incidence is incompletely understood. Females have a stronger immune response compared with males <sup>3,4</sup>. Such differences could be caused by sex hormones. The role of sex hormones as triggers in SSc is not completely understood, and there is no data available in the literature on how exogenous hormonal therapies could impact the development of scleroderma.

Here we describe three patients, all who met the ACR/EULAR 2013 criteria for SSc. These patients developed the disease following male-to-female transition, from our cohort of more than 2000 patients reviewed at our Centre. All patients had started their transition before the onset of the disease, and had not been diagnosed with any autoimmune disease before either starting the hormonal therapy (HT) required for the transition, or undergoing plastic surgery interventions. We also provide a critical appraisal of other published cases describing connective tissue diseases diagnosed after gender transition.

## **Patients and methods**

### **Case 1**

Case 1 was diagnosed age 35 years with diffuse cutaneous SSc, having started her transition five years before. At the beginning of her transition she started combination HT with mestranol and norethisterone (Norinyl-1®). Her first surgical intervention, buttock implants, occurred one

year prior to her diagnosis. This was unfortunately complicated by post-surgical infection and near extrusions. Two months after completing her antibiotic course she developed Raynaud's phenomenon and a vasculitic rash over arms and breasts. Antinuclear antibodies (ANA) were positive with a fine speckled pattern, which was subsequently identified as anti-RNA-polymerase III (ARA). She was treated with steroids and azathioprine. She had disease progression with skin thickening, vascular involvement with digital ulcers, gastroesophageal reflux disease (GERD), pulmonary arterial hypertension and telangiectasias. Approximately one year after the surgery she developed scleroderma renal crisis. She required chronic dialysis and was treated with mycophenolate mofetil (MMF), rapamycin, bosentan and proton-pump inhibitors (PPI). She eventually died 8 years after the diagnosis due to kidney and heart impairment. In this case we cannot rule out the contribution of the silicone buttock implants nor the contribution of post-surgical infection in the development of the disease.

## **Case 2**

The second patient was diagnosed with SSc at the age of 49 years, approximately six months after her gender reassignment surgery (removal of external genitalia and testicles), and five years after having started HT. Her HT consisted initially of conjugated oestrogens isolated from pregnant mares (Premarin®), and later with ethinylestradiol and gestodene (Femodene®). At disease onset she developed pain and stiffness of hands and wrists. Concomitantly, she developed Raynaud's phenomenon with puffy fingers, dysphagia, GERD and reduced exercise tolerance. ANA was negative, whereas anti-cytrullinated cyclic peptide antibody and rheumatoid factor were positive. She was initially diagnosed with inflammatory arthritis and was treated with methotrexate with only partial response. She then developed interstitial lung disease (ILD) with lower mid zone patchy changes, ischaemia of the index finger and distal skin thickening (modified Rodnan skin score of 8). The nailfold capillaroscopy showed an active scleroderma pattern. A diagnosis of limited cutaneous systemic sclerosis/rheumatoid arthritis overlap syndrome was

made and she was started on MMF, PPI, calcium-channel blocker (CCB) and low-dose steroid therapy with good response. At her latest follow-up appointment, 11 years after the diagnosis, the patient was still on low-dose MMF with partial regression of her skin involvement (modified Rodnan skin score of 4), no tender nor swollen joints, and stability of her lung involvement.

### **Case 3**

The third patient was diagnosed at the age of 43 years, two years after having started triptorelin (Decapeptyl®) and oestradiol valerate. She had not undergone any surgical intervention prior to her diagnosis. She developed anti-PM/Scl positive limited cutaneous SSc/myositis overlap syndrome and experienced Raynaud's phenomenon, GERD, and ILD. The nailfold capillaroscopy showed early scleroderma pattern. She was initially treated only with PPI and CCB prior to her breast reconstructive surgery. At her latest follow-up appointment, after she had undergone reconstructive surgery, she was started on MMF and steroid therapy with improvement of her muscle inflammation.

### **Discussion**

We report a case series describing transgender patients developing SSc after their transition to female. Key patient characteristics are summarized in Table 1. There are several aspects of the transition process that may be germane to the development of scleroderma, based upon its known complex pathogenesis that involves host and environmental factors. Although genetic aspects of disease susceptibility are not altered, it is possible that gender change has an effect on genetic and epigenetic (microRNAs, histone modifications, acetylation) factors<sup>5</sup> that themselves interact with hormonal aspects of gender transition. In two cases the patients had preceding surgery, either silicone implants (SI) or gender reassignment surgery, before the onset of SSc. The first patient had (SI) complicated by post-operative infection, and therefore we cannot rule out the role

that these implants may have played in triggering the disease, although previous studies have not supported such an association <sup>6</sup>. A cohort study has found an association between ARA positive dcSSc and SI <sup>7</sup>. Interestingly, the same antibody was found in our patient. In the two remaining cases no previous history of silicone exposure could be found, and in one case the onset of SSc preceded any surgery.

All patients had been started on HT before disease diagnosis. The specific type and duration of HT preceding disease onset differed in all patients. All patients were started on oestrogen therapy combined with either progestins or gonadotropin-releasing hormone agonist (Table 1). It is interesting to speculate that androgen reduction, achieved by GnRH agonist or bilateral orchiectomy, could have been the ultimate trigger for development of SSc, as in our cases this therapy was more closely temporally related to the onset of SSc. It is conceivable that an imbalance in the sex hormones could at least provide the predisposition to development of SSc. There is a wealth of data that affirms that sex hormones regulate multiple facets of the immune system. Oestrogens can influence the maturation of both T and B lymphocytes <sup>3</sup>, favour a Th2 response <sup>8</sup>, help autoreactive lymphocytes to escape from negative selection, increase autoantibody production <sup>9</sup>, stimulate cytokines release <sup>10</sup>, and induce the expression of perforin on Treg cells <sup>11</sup>. Oestrogens can also upregulate the activity of antigen-presenting cells and affect vascular endothelial cells having both local and systemic effects on target tissues <sup>12</sup>. Altered activation of the intracellular oestrogen pathway may also modulate the outcome of immune or autoimmune responses. Androgens can reduce antibody production, augment activation of CD8+ cells and enhance a Th1 response, specifically leading to increased IL-2 production <sup>3</sup>.

It is not known whether restoring the hormonal balance could be beneficial in reverting these changes. Once transgender patients have started their transition, it is challenging to offer the option of stopping HT, as it has been, and still remains, a crucial part of the transitional process. It is also worth considering that imbalances in the sex hormones have already been described in

small cohorts of scleroderma patients. From these studies it has emerged that SSc patients may have lower levels of androgens compared to normal controls <sup>13</sup>. Although further confirmatory studies are required, they suggest that sex hormones in SSc could play a role in the development of the disease, most likely though only in genetically susceptible individuals. There is no available evidence that transgender patients have a higher incidence of autoimmune diseases, especially scleroderma, but epidemiological studies focusing on autoimmunity have not been carried out in this population. In the English literature only 2 cases of transgender patients developing SLE after transition are described <sup>14,15</sup>. In both cases the patients had started the HT prior to the onset of their disease, and one had had also gender reassignment surgery (Table 1).

## **Conclusions**

This case series suggests that the hormonal modification as part of gender transition may be relevant in development of SSc. From our small cohort the clinical features, as well as the autoantibody profile were extremely heterogeneous. Further studies on hormonal interplay are required to better understand and predict the hormonal-mediated immunomodulatory effects in SSc. Unfortunately, it is hard to tell whether restoring the previous sex hormone balance could be of any benefit in this population of SSc patients. The therapeutic approach to our cohort did not differ from standard of care for SSc patients. As at present there is no evidence to guide continuation or cessation of hormonal therapies in this subgroup of patients, HT was continued in all cases. It is crucial to highlight that specific attention should be given to these patients and their families because of their complex psychological transitional path.

## **ACKNOWLEDGMENTS**

Lauren V Host is supported jointly by an educational research grant by the Australian Rheumatology Association (ARA), Roche, Arthritis Australia and ARA Western Australia.

## REFERENCES

1. Denton CP. Advances in pathogenesis and treatment of systemic sclerosis. *Clin Med (Lond)* 2016; 16(1): 55-60.
2. Barnes J, Mayes MD. Epidemiology of systemic sclerosis: incidence, prevalence, survival, risk factors, malignancy, and environmental triggers. *Curr Opin Rheumatol* 2012; 24(2): 165-70.
3. Pennell LM, Galligan CL, Fish EN. Sex affects immunity. *J Autoimmun* 2012; 38(2-3): J282-91.
4. D'Amico F, Skarmoutsou E, Mazzarino MC. The sex bias in systemic sclerosis: on the possible mechanisms underlying the female disease preponderance. *Clin Rev Allergy Immunol* 2014; 47(3): 334-43.
5. Khan D, Dai R, Ansar Ahmed S. Sex differences and estrogen regulation of miRNAs in lupus, a prototypical autoimmune disease. *Cell Immunol* 2015; 294(2): 70-9.
6. Janowsky EC, Kupper LL, Hulka BS. Meta-analyses of the relation between silicone breast implants and the risk of connective-tissue diseases. *N Engl J Med* 2000; 342(11): 781-90.
7. Saigusa R, Asano Y, Nakamura K, et al. Association of anti-RNA polymerase III antibody and silicone breast implants in patients with systemic sclerosis. *J Dermatol* 2016; 43(7): 808-10.
8. Hill L, Jeganathan V, Chinnasamy P, Grimaldi C, Diamond B. Differential roles of estrogen receptors alpha and beta in control of B-cell maturation and selection. *Mol Med* 2011; 17(3-4): 211-20.
9. Pauklin S, Sernandez IV, Bachmann G, Ramiro AR, Petersen-Mahrt SK. Estrogen directly activates AID transcription and function. *J Exp Med* 2009; 206(1): 99-111.

10. Fish EN. The X-files in immunity: sex-based differences predispose immune responses. *Nat Rev Immunol* 2008; 8(9): 737-44.
11. Valor L, Teijeiro R, Aristimuno C, et al. Estradiol-dependent perforin expression by human regulatory T-cells. *Eur J Clin Invest* 2011; 41(4): 357-64.
12. Foresta C, Zuccarello D, Biagioli A, et al. Oestrogen stimulates endothelial progenitor cells via oestrogen receptor-alpha. *Clin Endocrinol (Oxf)* 2007; 67(4): 520-5.
13. Mirone L, Altomonte L, D'Agostino P, Zoli A, Barini A, Magaro M. A study of serum androgen and cortisol levels in female patients with rheumatoid arthritis. Correlation with disease activity. *Clin Rheumatol* 1996; 15(1): 15-9.
14. Chan KL, Mok CC. Development of systemic lupus erythematosus in a male-to-female transsexual: the role of sex hormones revisited. *Lupus* 2013; 22(13): 1399-402.
15. Santos-Ocampo AS. New onset systemic lupus erythematosus in a transgender man: possible role of feminizing sex hormones. *J Clin Rheumatol* 2007; 13(1): 29-30.

## Table

Table 1. Characteristics of transgender SSc patients and transgender SLE patients

| Patient | Age (years) | Diagnosis        | Antibody                                       | Organ involvement            | Hormonal therapy  | Duration of HT | Surgery prior to diagnosis | Therapy                           |
|---------|-------------|------------------|--|------------------------------|---|----------------|----------------------------|-----------------------------------|
| 1       | 35          | dcSSc            | Anti-RNA polymerase III                        | RP, DU, GERD, PAH, SRC       | Mestranol and norethisterone                            | 5 years        | Buttock implants           | CS, MMF, Bosentan, PPI            |
| 2       | 49          | lcSSc/RA overlap | ANA negative<br>ACPA and RF positive           | IA, dysphagia, GERD, ILD, DU | Conjugated oestrogens<br>Ethinylestradiol and gestodene | 5 years        | Gender reassignment        | MTX, MMF, PPI, CCB, CS            |
| 3       | 43          | lcSSc/PM overlap | Anti-PM/Scl                                    | RF, GERD, ILD, myositis      | Triptorelin and oestradiol valerate                     | 2 years        | No                         | PPI, CCB, MMF, CS                 |
| 4 [14]  | 43          | SLE              | Anti-U1RNP<br>Anti-Sm<br>Anti-Ro<br>Anti-dsDNA | Neuropsychiatric, DVT        | Conjugated oestrogens                                   | 17 years       | Gender reassignment        | Immunosuppression (not specified) |
| 5 [15]  | 23          | SLE              | Anti-U1RNP<br>Anti-Sm<br>Anti-Ro<br>Anti-La    | GMN                          | "hormonal shots"  | 1 year         | No                         | IVMP, CYC                         |

RP = Raynaud's phenomenon; DU = digital ulcer; GERD = gastro-oesophageal reflux disease; IA = inflammatory arthritis; ILD = interstitial lung disease; GMN = glomerulonephritis; CS = corticosteroid; MMF = mycophenolate mofetil; PPI = proton pump inhibitor; CCB = calcium channel blocker; IVMP = IV methylprednisolone; CYC = cyclophosphamide