Case Report

Lupus nephritis in a transgender woman on cross-sex hormone therapy: a case for the role of oestrogen in systemic lupus erythematosus

Lupus
2020, Vol. 29(13) 1807–1810

DOI: 10.1177/0961203320946372
journals.sagepub.com/home/lup
SAGE

Brittany G Hill, Bonnie Hodge and Richard Misischia

Abstract

We present the case of a 22-year-old African American transgender women (male to female), who was admitted for fatigue, abdominal pain and lower extremity edema and was diagnosed with systemic lupus erythematosus (SLE) and lupus nephritis. Treatment with high-dose steroids and mycophenolate mofetil helped resolve her symptoms. She has remained off oestrogen therapy since admission and has not experienced any major complications. It is important to consider therapy outcomes in this specific patient population. A review of four other cases of transgender women on cross-sex hormone therapy who were diagnosed with lupus is also presented.

Keywords

Systemic lupus erythematosus, nephritis, estrogen, transgender, renal lupus

Date received: 21 May 2020; accepted: 9 July 2020

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that causes chronic inflammation of the major organ systems. The disease is characterized by the production of autoantibodies that cause immune complex formation and deposition in tissue, resulting in inflammation and organ damage. Lupus nephritis is a common complication of SLE in which inflammation and damage to the kidneys occur.

Individuals identifying as transgender often use cross-sex hormone therapy before, during and/or after sex reassignment. The predilection of SLE in pre-menopausal women compared with men is profound. There is an established link between estrogen and SLE, but the exact cause is unknown. Interestingly, other pathological states with abundant estrogen levels or a lack of androgen also have a correlation with the disease. Patients receiving estrogen therapy before or after sexual reassignment surgery represent a unique population. It is important to recognize the gender differences in SLE and to explore the most effective management in patients desiring cross-sex hormone therapy.

Case

A 22-year-old African American transgender woman (male to female) with a history of hypertension presented with diffuse abdominal pain, fatigue and lower-extremity oedema for several weeks. She had been taking cross-sex hormones for nearly two years but had not scheduled sex reassignment surgery due to cost. On physical exam, she was tachycardic (102 bpm) and mildly hypertensive (140/87 mmHg). Her abdomen was distended, and she had diffuse tenderness on palpation, with pitting edema to the knees

Department of Internal Medicine, Brookwood Baptist Health Birmingham, Alabama, USA

Corresponding author:
Brittany Hill, Department of Internal Medicine, Brookwood Baptist Health, 701 Princeton Avenue SW, Birmingham, AL 35211, USA.
Email: brittany.hill@bhsala.com

Table 1. Review of published cases involving transgender women with lupus on oestrogen therapy.

Case	Presentation	Duration on oestrogen therapy	Serology	Lupus nephritis	Treatment	Outcome
Santos-Ocampo (2007)	Congestive heart failure, pericardial effusion, pulmonary infiltrates, anaemia, renal insufficiency, proteinuria; no previous lupus diagnosis	1 year	ANA 1:2560, speckled +anti-Sm +anti-U1RNP +anti-SSA +anti-SSB –anti-dsDNA –anti-GBM Ab Low complement levels	Diffuse proliferative glomerulonephritis	i.v. methylprednisone 100 mg for 4 weeks i.v. CYC 500 mg 1 dose	Complete response; off dialysis; complement normalized
Zandman-Goddard (2007)	Diffuse rash (face, chest, back); weakness, arthritis, chest pain, mood disturbances; no previous lupus diagnosis	7 years+sex reassignment surgery+silicone augmentation mammoplasty	ANA negative –anti-dsDNA –anti-SSA/Ro –anti-RNP –anti-smooth muscle Ab Normal complement –ANCA	None	p.o. hydroxychloroquine 200 mg b.i.d.	Improvement of cutaneous and joint manifestations
Chan (2013)	Psychosis, recent deep-vein thrombosis; no previous lupus diagnosis	20 years+sex reassignment surgery	ANA 1:2560, homogenous +anti-dsDNA +anti-Sm +anti-SSA/Ro –lupus anticoagulant –anticardiolipin IgG/IgM –anti-B2-glycoprotein	None	Immunosuppression, antipsychotics	Improvement of mental status
Pontes (2018)	Lower-limb oedema, malar rash, photosensitivity, anaemia, renal insufficiency, proteinuria; no previous lupus diagnosis	9 years+sex reassignment surgery	+ANA +anti-dsDNA +anti-SSA/Ro Low complement levels	Diffuse proliferative glomerulonephritis and granular immune complex deposits with a 'full-house' pattern	i.v. methylprednisone 1 g/day for 3 days, p.o. prednisone 1 mg/kg/day over weeks; i.v. CYC CYC 1 g monthly for 6 months; 6 months later, MMF 3 g	Complete response
Our case (2020)	Abdominal pain, anaemia, renal insufficiency, proteinuria; no previous lupus diagnosis	2 years	+ANA +anti-dsDNA +anti-Sm Low complement levels	Membranous lupus nephritis with granular immune complex deposits with a 'full-house' pattern	i.v. methylprednisone 1 g/day for 3 days, p.o. prednisone 1 mg/kg/day over weeks; MMF	Complete response

MMF: mycophenolate mofetil; CYC: cyclophosphamide; i.v.: intravenous.

bilaterally. Initial laboratory results revealed 2+ proteinuria, profound hypoalbuminaemia, mild normocytic anaemia (consistent with anaemia of chronic disease) and elevated creatinine. A computed tomography scan of the abdomen and pelvis showed diffuse ascites, anasarca and a left pleural effusion. Protein-losing nephropathy was suspected and confirmed with a protein-to-creatinine ratio of 9000:1 and a total protein of 845 (nephrotic-range proteinuria quantified by spot urine polymerase chain reaction and confirmed by 24-hour collection). Serologies, positive for ANA, anti-dsDNA and anti-Sm antibodies prompted a diagnosis of SLE, which was also supported by a low C3 level. Other etiologies of nephrotic syndrome, including hepatitis B and C, human immunodeficiency virus, cryoglobulinaemia and ANCA-related diseases, were ruled out. A renal biopsy was subsequently obtained which demonstrated class V lupus nephritis with a 'full house' immunofluorescence staining pattern (IgG, IgM, IgA, C3 and kappa and lambda light chains). The patient was started on prednisone, mycophenolate mofetil and trimethoprim sulfamethoxazole. Spironolactone, a component of her cross-sex hormone therapy, was reduced from 50 to 25 mg b.i.d. Throughout the hospital course, the edema and abdominal pain improved, and serum creatinine eventually normalized. She was discharged on a 6-month steroid taper and has not had any major complications.

Discussion

As of 2018, only four cases of SLE in transgender women on hormone therapy have been reported, three of which occurred after sex reassignment surgery (gonadectomy). The cases represented in Table 1 show the deleterious effects of estrogen in transgender women without a previous lupus diagnosis.[1–4]

Estrogen has been shown to promote the survival and stimulation of autoreactive B cells and increases the expression of a subset of IgG auto-antibodies specific for dsDNA.[5] Furthermore, estrogen prevents apoptosis of SLE-specific T cells by downregulating Fas ligand expression, thus lengthening T-cell survival.[6] The use of hormone replacement therapy in post-menopausal women causes a twofold increase in the risk of developing SLE compared with non-users.[7] Past users of oral contraceptive pills demonstrate a relative risk of 1.9 compared with those who have never used oral contraceptives.[8]

Studies conducted with murine models demonstrated that the castration of male mice and treatment with estrogen therapy rapidly escalated the timeline of SLE development similar to that of the female models. Castrated male murine models with a diagnosis of SLE also had accelerated development of lupus nephritis.[9] When males are diagnosed with SLE, they tend to have more severe disease (especially renal and cardiovascular) with faster rates of disease progression.[10] However, androgen therapy and estrogen receptor deficiency in murine models have a protective effect. This protective role strengthens the support that there is a link between estrogen and SLE.

These studies represent the importance of open communication between physician and transgender patients looking to start cross-sex hormone therapy. As evident by the aforementioned cases published regarding transgender women on estrogen therapy, the length of estrogen therapy seems to have no bearing on disease severity. In addition, there seems to be no association between hypertension and renal involvement in these cases. Only three of the cases had renal involvement, and none of the patients had ever had a previous lupus diagnosis. Further examination into the patients' family history could provide information about an autoimmune disease connection. However, this may or may not provide insight into long-term effects of estrogen therapy.

The relationship between the effects of estrogen in the pathogenesis of SLE has been previously established but is not completely understood. The importance of family history and perhaps autoimmune serology prior to cross-sex hormone therapy could prove helpful. In addition, withdrawal of estrogen therapy in the setting of severe SLE should be deliberated. Careful consideration of underlying genetic predisposition to SLE is crucial when treating patients who identify as transgender.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship and/or publication of this article.

ORCID iD

Brittany G Hill https://orcid.org/0000-0002-1317-4590

References

1. Santos-Ocampo AS. New onset systemic lupus erythematosus in a transgender man: Possible role of feminizing sex hormones. *J Clin Rheumatol* 2007; 13: 29–30.
2. Zandman-Goddard G, Solomon M, Barzilai A, Shoenfeld Y. Lupus erythematosus tumidus induced by sex reassignment surgery. *J Rheumatol* 2007; 34: 1938–1940.

3. Chan KL, Mok CC. Development of systemic lupus erythematosus in a male-to-female transsexual: The role of sex hormones revisited. *Lupus* 2013; 22: 1399–1402.
4. Pontes LT, Camilo DT, Bortoli MRD, et al. New-onset lupus nephritis after male-to-female sex reassignment surgery. *Lupus*; 27: 2166–2169.
5. Grimaldi CM, Cleary J, Dagtas AS, Moussai D, Diamond B. Estrogen alters thresholds for B cell apoptosis and activation. *J Clin Invest* 2002; 109: 1625–1633.
6. Kim WU, Min SY, Hwang SH, Yoo SA, Kim KJ, Cho CS. Effect of estrogen on T cell apoptosis in patients with systemic lupus erythematosus. *Clin Exp Immunol* 2010; 161: 453–458.
7. Sánchez-Guerrero J, Liang MH, Karlson EW, Hunter DJ, Colditz GA. Postmenopausal estrogen therapy and the risk for developing systemic lupus erythematosus. *Ann Intern Med* 1995; 122: 430–433.
8. Sanchez-Guerrero J, Karlson EW, Liang MH, Hunter DJ, Speizer FE, Colditz GA. Past use of oral contraceptives and the risk of developing systemic lupus erythematosus. *Arthritis Rheum* 1997; 40: 804–808.
9. Roubinian JR, Talal N, Greenspan JS, Goodman JR, Siiteri PK. Effect of castration and sex hormone treatment on survival, anti-nucleic acid antibodies, and glomerulonephritis in NZB/NZW F1 mice. *J Exp Med* 1978; 147: 1568–1583.
10. Crosslin KL, Wiginton KL. Sex differences in disease severity among patients with systemic lupus erythematosus. *Gender Med* 2011; 8: 365–371.