A 31-year-old woman presented with secondary amenorrhoea and inability to conceive, which was of 3 years duration. She had Raynaud’s phenomenon for 16 years, primary hypothyroidism for 5 years, digital ulcers for 4 years and skin tightening for 2 years. She had an expressionless face, with loss of wrinkles and restriction of the mouth opening along with flexion contractures of the hands and the terminal digit resorptions. Investigations showed Antinuclear antibodies (ANA) and anti-Scl 70 positivity confirming the presence of systemic sclerosis (SSc). The Follicle Stimulating Hormone (FSH) level was elevated, the ovarian follicles were absent, and the endometrial thickness was reduced confirming premature ovarian failure (POF). POF causing infertility and secondary amenorrhoea in SSc is an unusual manifestation; moreover, POF occurred without the involvement of other internal organs.

KEYWORDS: Amenorrhoea, infertility, menopause, premature ovarian failure, scleroderma, systemic sclerosis

INTRODUCTION

Systemic sclerosis (SSc) is a complex autoimmune connective tissue disorder with a prevalence of five per 100,000 and an incidence of one per 100,000.[1] The skin is invariably involved, but commonly affected internal organs include the cardiovascular system, the lungs and the gastrointestinal system. However, uncommon manifestations present clinical dilemmas. This case of SSc describes the unique involvement of the ovaries leading to premature ovarian failure (POF), without the involvement of any other internal organs.

CASE REPORT

A 31-year-old woman, parity one (full-term, normal vaginal delivery), with no abortions presented with inability to conceive and amenorrhoea of 3 years duration. She had Raynaud’s phenomenon for 16 years, primary hypothyroidism for 5 years (though euthyroid on treatment with thyroxine 100 μg once daily), digital ulcers for 4 years and shortening of the terminal digits, decreased mouth opening and skin tightening for 2 years.

There was no history of fever, weight loss, anorexia, sleep disturbance, symptoms of the respiratory, the cardiovascular, the gastrointestinal or the nervous system involvement, or the intake of any drugs (apart from thyroxine) or substance abuse.

She had an expressionless face [Figure 1], with loss of wrinkles, a taut and shiny skin, a reduced oral aperture (permitting only two fingers) and a pinched beak-like nose. The skin over the upper and the lower limbs was shiny and thickened. There was fixed flexion contracture of the fingers of the upper limbs [Figure 2] and amputation of the 2nd digit of the left lower limb [Figure 3]. The rest of the general physical and systemic examination including gynaecological examination was normal.

Investigations revealed the following: haemoglobin – 8.6 g/dL, Total leucocyte count (TLC) – 4.6 × 10³/mm³, platelet count – 1.01 × 10⁵/mm³ and Erythrocyte Sedimentation Rate (ESR) – 75 mm at the end of the 1st hour; the liver and the kidney functions and blood sugar were normal. Urine pregnancy test was negative.

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How to cite this article: Nigam A, Prakash A, Sharma S, Kumar N. Premature Ovarian Failure – An Unusual Manifestation of Systemic Sclerosis. J Hum Reprod Sci 2017;10:58-60.
Electrocardiogram, echocardiography, chest X-ray and pulmonary function test parameters were also normal. Serum TSH level was 4.61 μIU/mL (normal 0.34–5.6 μIU/mL), and anti-thyroid antibodies were negative.

The following serum immunohistochemistry findings were suggestive of SSc: positive ANA (by Indirect Immunofluorescence, at 1:100 dilution), 3+ positivity for Scl-70, anti-dsDNA by ELISA was 24 IU/mL (normal value <25), and p-ANCA, c-ANCA and anti-LKM were negative.

Ultrasonography revealed the presence of normal-sized ovaries (left 2 cm × 1.8 cm × 1 cm and right 2.4 cm × 2 cm × 0.8 cm) with absent ovarian follicles and normal-sized uterus (7.2 cm × 5.4 cm × 3.6 cm), with an endometrial thickness of 3 mm (with normal being more than 4–5 mm). Serum FSH level was 125.6 and 130 IU/L on two separate occasions 1 month apart (normal 1–10 IU/L), and serum Luteinizing Hormone (LH) level was 56.42 IU/L (normal 1.68–15 IU/L), suggesting ovarian failure.

A diagnosis of SSc was made on the basis of the characteristic clinical features on history taking and examination and positive serum immunohistochemistry; secondary amenorrhoea was attributed to POF.

**DISCUSSION**

Fertility issues in the patients with SSc have been debated over decades. It is surmised that the deleterious effects of SSc begin long before conception because of several reasons. The reasons include the psychosocial issues of reduced self-esteem and altered body image arising as a result of skin discolouration and hardening, perioral skin tightening, finger lesions, and digit amputation, as well as because of physical ailments namely vaginal dryness, dyspareunia, arthritic involvement and contractures.[2]

In a comprehensive paper published at the turn of the century, it was reported that fertility in the patients with SSc was not significantly different from that in patients with rheumatoid arthritis and the healthy control population, when adjustments were made for possible contributing factors.[3] POF is a cessation of the ovarian function before the age of 40 years, and it may occur due to chromosomal causes (Turner syndrome and fragile X syndrome), iatrogenic causes (radiation, chemotherapy and surgery), infections, autoimmune disorders, galactosemia,
Savage syndrome, cigarette smoking, etc. POF occurs in <1% of women; its incidence is about one in 1000 women by the age of 30 years, one in 250 by the age of 35 years and one in 100 by the age of 40 years. Depending on various studies, autoimmunity may be responsible for POF in 4–30% of the cases. The evidence of autoimmunity in these cases is suggested by the presence of ovarian autoantibodies, lymphocytic oophoritis or other autoimmune disorders. The former two conditions are difficult to assess because of the absence of sensitive and specific tests to measure ovarian autoantibodies. Ovarian biopsy is not recommended due to unknown clinical value and risks involved. Hypothyroidism, diabetes mellitus and Addison disease are the common autoimmune disorders associated with POF.

There are very few reports in which premature menopause has been reported in the patients with SSc. Way back in 1983, by observing the age of menopause in patients with scleroderma, it was reported that the ovaries were not involved in scleroderma. However, in 1995, among 60 patients with scleroderma, vaginal dryness, ulceration, dyspareunia and many menstrual abnormalities were observed, but premature menopause was seen in only two patients at the ages of 29 and 38 years, respectively. Vural et al. reported POF in a 25-year-old woman with localized scleroderma. However, a recent study in 2012 stated that scleroderma does not cause POF unless treated with alkylating agents such as cyclophosphamide.

This patient had marked digital ulcerations and also loss of the digits, depicting severe peripheral vascular involvement, which is reflective of a systemic involvement. However, there was no involvement of the visceral organs, that is, the heart or the lungs, in this patient, although the ovaries were involved, which is very rare and unusual. The inflammation and microvascular damage to the ovaries might have resulted in POF in this case, but in the absence of any other visceral organ involvement, it is very difficult to comment on the exact mechanism.

The study of POF as a cause of infertility in the patients with SSc is important, because it is irreversible and can save the couple from unnecessary investigations and psychological trauma. Moreover, early menopause in the patients with SSc predicts pulmonary hypertension, which is one of the causes of mortality in these patients. Additionally, menopause per se has an additive effect on the risk for common co-morbidities such as cardiovascular disease and osteoporosis.

**CONCLUSION**

POF can be a possible cause of amenorrhoea in the patients with SSc, and it can be a poor predictor of disease progression. Further, the link of POF needs to be correlated with other complications of SSc.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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