



## Case reports

## Scleroderma renal crisis and ovarian hyperstimulation syndrome related to the use of clomiphene in a patient with scleroderma

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## ABSTRACT

This paper presented a 28-year-old female with systemic sclerosis who developed scleroderma renal crisis and ovarian hyperstimulation syndrome following clomiphene administration. Urgent therapy including angiotensin-converting enzyme (ACE) inhibitors and supportive care resulted in regression and eventually resolution of all the clinical and laboratory symptoms. Although scleroderma renal crisis is a fatal complication of high-dose corticosteroids, rarely is this seen with the use of ACE inhibitors. This case report aimed to investigate the potential capacity of the selective oestrogen receptor modulator clomiphene to induce scleroderma renal crisis as well as corticosteroids.

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### Crisis renal por escleroderma y síndrome de hiperestimulación ovárica relacionados al uso de clomifeno en una paciente con escleroderma

## RESUMEN

Se presenta el caso de una mujer de 28-años de edad con esclerosis sistémica que desarrolló una crisis renal y un síndrome de hiperestimulación ovárica después de la administración de clomifeno. Se le dio tratamiento urgente con inhibidores de la enzima convertidora de angiotensina (ECA) y cuidados de apoyo que resultaron en la regresión y, finalmente, la resolución de todos los síntomas clínicos y de laboratorio. La crisis de esclerodermia renal es una complicación mortal del uso de altas dosis de corticosteroides, que rara vez se ve con el uso de inhibidores de la ECA. Este caso tuvo como objetivo investigar el potencial del modulador del receptor de estrógenos, clomifeno, para inducir una crisis renal por esclerodermia en una manera similar a los corticosteroides.

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## Introduction

Systemic sclerosis is a chronic inflammatory disease characterized by dermal and visceral fibrosis, often accompanied by obliterative vasculopathy.<sup>1,2</sup> In addition, scleroderma renal crisis (SRC) is a rare, but fatal complication related to a sudden onset of malignant hypertension.<sup>3</sup> The most common signs and symptoms include renal dysfunction, stroke and cardiac arrhythmias. The considered sustained activation of renin–angiotensin–aldosterone axis may be responsible for this complication.<sup>4</sup> Although the mortality rates were higher in the previous years, with the use of angiotensin

converting enzyme (ACE) inhibitors today, it accounts for only <5% of the cases.<sup>5</sup> Corticosteroids are well-known anti-inflammatory agents that induce SRC.<sup>6</sup> High-dose corticosteroid use is associated with SRC. Clomiphene is an agent used for ovarian stimulation. Despite rarely seen, ovarian hyperstimulation syndrome (OHSS), characterized by ascites, ovarian enlargement, pleural effusion and hypovolemia may develop with the use of clomiphene.<sup>7</sup> Review of the literature did not show any association between SRC and clomiphene use. In this paper, we present a case with SRC and OHSS related to the use of clomiphene.

## Case report

In April 2011, a 28-year-old woman visited our rheumatology clinic complaining of severe nausea and vomiting, headache and

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sudden changes in her conscious state during the previous two weeks. The patient's history revealed that in 2007, she presented with swelling in the hands, morning stiffness lasting more than an hour, symmetric skin thickening proximal to the metacarpophalangeal joints and Raynaud's Phenomenon. The rheumatologist then gave a diagnosis of scleroderma. The patient was given an individual treatment including methotrexate (10 mg/week), methylprednisolone (4 mg/day), enalapril (5 mg/day), nifedipine (60 mg/day) and acetylsalicylic acid (100 mg/day) and she attended all scheduled visits over four years with full patient compliance. During one such visit in January 2011, the patient informed her physician that she was planning to get pregnant. Immediately all but one of the medications (acetylsalicylic acid 100 mg daily) were discontinued. The patient visited the Gynecology and Obstetrics Clinic where she was prescribed clomiphene 100 mg/day for ovarian stimulation in March 2011. She experienced nausea, vomiting and severe headache three weeks later. Symptomatic treatment given by her physician did not provide any relief and therefore, she was referred to our rheumatology clinic in April 2011. A physical examination revealed sclerodactylia of the fingers, Raynaud's phenomenon; severe skin thickness involves the proximal extremities and/or the trunk in addition to distal thickening and facial telangiectasia. Blood pressure was 200/110 mmHg and body temperature was 36.8 °C. At the time of admission, laboratory tests revealed newly developed microangiopathic haemolytic anaemia (MAHA) with fragmented red blood cells, haemoglobin 7.8 g/dl, hematocrit 27 mg/dl, reticulocytes 10%, thrombocytopenia (platelet count 130,000 mm<sup>3</sup>) and a marked increase in creatinine level 3.6 mg/dl. Urinalysis revealed proteinuria (0.5 g/24 h) and haematuria, with granular castes evident on microscopy. Tests for liver function, total cholesterol, blood glucose, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and estradiol 80.6 ng/dL (normal range <160 ng/dL) and beta-HCG <1.0 mIU/mL (negative 0–5.3), showed normal values. Anti nuclear antibodies were positive at a titer of 1:160 and test for anti-Scl-70 antibody was positive. Rheumatoid factor, anti-dsDNA antibody, C3, C4, anticardiolipin antibody (ACA) IgG and IgM were negative. Chest X-ray also revealed minimal pleural effusion in the left side. Echocardiographic examination demonstrated a non-compressive minimal pericardial effusion. Results from the cranial MRI were found to be normal. The patient was referred to the Neurology Clinic with a suspicion of encephalopathy and proposed anti-hypertensive treatment. The consultant Ophthalmologist also diagnosed hypertensive retinopathy. Abdominal ultrasonography showed increased bilateral renal parenchymal echogenicity, which was consistent with type one renal parenchymal disease. Colour Doppler ultrasonography demonstrated bilateral ovarian enlargement including the largest ones with anechoic mass with regular contours 63 mm × 60 mm (right) and 57 mm × 52 mm (left). Colour Doppler ultrasonography also showed a few cysts without prominent vascularization. Following the abdominal ultrasonography, the patient was referred to the Gynecology and Obstetrics Clinic. Transvaginal ultrasonography showed a normal uterus, endometrial menstrual cycle, two follicles in the right ovary (6.8 cm × 5.8 cm and 1.55 cm) and in the left ovary (3.5 cm × 2.3 cm and 3.8 cm × 2.5 cm) containing free fluid in the pouch of Douglas. The test results of estradiol and beta-HCG were evaluated together and when these findings indicated OHSS related to the use of clomiphene, supportive care and fluid-electrolyte therapy were administered. All clinical and laboratory findings were assessed and a therapy including ACE inhibitors and a calcium channel blocker were prescribed for the management of hypertensive SRC with regular monitoring. On day five, the patient's blood pressure dropped to 130/90 mmHg and symptomatic relief was maintained in terms of headache, nausea and vomiting on day 7. Repeated laboratory tests at the end of the first month showed improved renal parameters: blood urea nitrogen (BUN) 20 mg/dl

and creatinine 2.6 mg/dl. At the end of 3 months, the symptoms were completely resolved and the test results were as follows: BUN 25 mg/dl, creatinine 1.4 mg/dl, serum albumin 3.5 g/l, haemoglobin 10.6 g/dl, haematocrit 31.5 mg/dl, platelet counts 165,000/mm<sup>3</sup>. Acute phase reactants (erythrocyte sedimentation rate and C-reactive protein) and urinalysis showed normal values. Control chest X-ray, abdominal ultrasonography, and echocardiography indicated normal findings.

## Discussion

In this study, we evaluated a case with diffuse scleroderma developing OHSS and SRC related to the use of clomiphene, which was given for ovarian stimulation. Urgent therapy including ACE inhibitors and supportive care resulted in regression and eventually resolution of all the clinical and laboratory symptoms.

Systemic sclerosis is a chronic autoimmune disease that is characterized by dermal and visceral fibrosis, often accompanied by obliterative vasculopathy. SRC, Raynaud's phenomenon, and pulmonary arterial hypertension are the most common complication of vascular involvement. SRC is commonly seen in female patients with diffuse scleroderma using corticosteroids. Sudden onsets of moderate to severe hypertension and related acute renal insufficiency, encephalopathy or cardiac arrhythmias are the most significant predictors of mortality.<sup>8</sup> The use of ACE inhibitors in rheumatology practice is the major approach in decreasing the mortality rate from 42% to 6%.<sup>9</sup> Although the underlying pathogenesis is still unknown, it is believed narrowing of the renal interlobular and arcuate arteries and endothelial damage are possible mechanisms. In addition, fibrosis and epithelial and mesenchymal transdifferentiation of the glomerular and tubulointerstitial compartments as well as dysregulation of endothelin-1 receptor expression are among other mechanisms which have been suggested so far.<sup>10</sup> OHSS is a rare complication of ovulation induction with exogenous agents. The clinical presentations range from ascites, ovarian enlargement and pleural and/or pericardial effusion to electrolyte imbalance and hypervolemia.<sup>11</sup> Although the underlying pathogenesis is contradictory, several vasoactive cytokines which are released from ovaries and corpus luteum are considered to play a part in the etiology of the disease.<sup>12</sup> The possible role of vascular endothelial growth factor (VEGF) and vascular permeability factor (VPF), have been an issue of debate.<sup>13</sup> VEGF is an important antigenic cytokine with critical roles in ovarian angiogenesis, follicular growth, and the proper function of corpus luteum. It has been also shown that HCG administration leads to the increased expression of VEGF in the granulosa-lutein cells.<sup>14</sup> It has also been suggested that high level of VEGF, IL-6 and IL-8 level in the serum, peritoneal fluid and follicular fluid is associated with the development of OHSS and severity of the disease.<sup>15</sup> In our case the clinical, radiological and laboratory findings confirmed the diagnosis of OHSS. Interestingly, the patient had hypertension, but not hypotension, due to concomitant SRC, which both had different underlying mechanisms. OHSS identified by increased capillary permeability, resulting in leakage of fluid from the vascular compartment, with third-space fluid accumulation and intravascular dehydration. In this case, ascites and pleural and pericardial effusions were observed. However, although hypotension was present due to hypovolemia, the patient also presented with symptoms of malignant hypertension due to SRC. It may be explained by the possible association between SRC with increased serum ACE and renin level.<sup>16</sup> Therefore, a dramatic response to ACE inhibitors took place. A review of the literature revealed a case with OHSS related to the use of clomiphene with an increased serum ACE level.<sup>16</sup> It is considered that increased serum ACE level is an important underlying mechanism of the pathogenesis of OHSS. Reports show

that patients with polycystic ovary syndrome may have increased prorenin levels known as a risk factor for OHSS.<sup>17</sup> Gonadotropin hormones and/or clomiphene used for ovarian stimulation also increase prorenin levels. In addition, it has been well documented that active renin and angiotensin-II levels are elevated by ovarian stimulation.<sup>18–20</sup>

In conclusion, we have presented a case of scleroderma developing OHSS accompanied by SRC related to the use of clomiphene. Although our case report presents important evidence to the etiopathogenesis of SRC seen in the patients with scleroderma, large-scale studies are further required to shed light on the nature of the pathogenesis of SRC and possible risk factors for the disease.

### Ethical disclosures

**Protection of human and animal subjects.** The authors declare that the procedures followed were in accordance with the regulations of the responsible Clinical Research Ethics Committee and in accordance with those of the World Medical Association and the Helsinki Declaration.

**Confidentiality of data.** The authors declare that they have followed the protocols of their work centre on the publication of patient data and that all the patients included in the study have received sufficient information and have given their informed consent in writing to participate in that study.

**Right to privacy and informed consent.** The authors have obtained the informed consent of the patients and/or subjects mentioned in the article. The author for correspondence is in possession of this document.

### Conflict of interest

The authors declare no conflict of interest.

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