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Case Report

Cardiac Transplant in Young Female Patient Diagnosed With Diffuse Systemic Sclerosis[☆]



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ABSTRACT

Systemic sclerosis (SS) is a multifactorial and systemic, chronic, autoimmune disease that affects the connective tissue. We present this clinical case given the low prevalence of diffuse SS with early and progressive cardiac compromise in a young patient, and treatment with cardiac transplantation.

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Trasplante cardíaco en una paciente joven con diagnóstico de esclerosis sistémica difusa

RESUMEN

La esclerosis sistémica (ES) es una enfermedad autoinmune, crónica, multifactorial y sistémica que afecta al tejido conectivo. Presentamos este caso clínico dado la baja prevalencia de ES difusa con compromiso cardíaco temprano y progresivo en una paciente joven, y tratamiento con trasplante cardíaco.

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Introduction

Systemic sclerosis (SS) is a multisystem autoimmune disease characterized by inflammation and excessive extracellular matrix deposition in skin and internal organs. The clinical course can range from that of a benign condition, with only cutaneous and peripheral vascular involvement to that of a rapidly progressive disease, affecting 1 or more internal organs. It is classified as localized (involving only the skin) or systemic. In turn, the systemic variant is subclassified as limited and diffuse, depending on the expanse of skin affected. The diffuse form is characterized by the rapid development of symmetrical skin thickening in the proximal and distal regions of the extremities, and in face and trunk.

This subgroup is positive for anti-topoisomerase 1 antibody (Scl 70) and is at higher risk of internal organ involvement in the initial phases of the disease. The limited form is defined by the development of symmetrical skin thickening confined to the distal regions of the extremities and the face. The patients test positive for the anti-centromere antibody and the prognosis is better except in those with pulmonary hypertension and biliary cirrhosis. The incidence of cardiac involvement is similar in the two forms of presentation, but is more severe in diffuse SS (DSS).¹ It can be a primary cause of – or secondary to – pulmonary hypertension, pulmonary interstitial disease and kidney disease, and can affect myocardium, the conduction system, pericardium and the valve apparatus.^{2,3}

Transthoracic echocardiography (TTE) should be a routine evaluation, in combination with electrocardiography and chest X-ray.⁴ Gadolinium-enhanced nuclear magnetic resonance imaging (MRI) characteristically shows “late linear and subendocardial enhancement” corresponding to the pattern of myocardial fibrosis. The T2-weighted images evaluate the presence of myocardial edema, characteristic of “scleroderma myocarditis”.⁵ Cardiac

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biopsy is pathognomonic and reveals “contraction band necrosis and replacement of the myocardial tissue by patchy fibrosis”.⁶

Among the treatments administered, calcium antagonists, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers were found to improve myocardial perfusion. Immunosuppression is proposed as an option in myocarditis. In the case of congestive heart failure (CHF) refractory to drug therapy, heart transplantation should be considered.⁷

We present the case of a young woman with a diagnosis of DSS, with early progressive cardiac involvement. The importance of this case lies in the form of presentation and its refractoriness to medical treatment, making heart transplantation necessary. We decided to perform a literature review and report this association, taking into account the limited number of references to this condition.

Case Report

A 19-year-old woman was referred to our service to be evaluated for DSS. Her medical history included CHF complicated by acute pulmonary edema, for which she had required several hospital stays over the preceding 5 months. Three years earlier, her condition had begun with rapidly progressing, generalized skin thickening, microstomia and Raynaud’s phenomenon, myalgia, muscle weakness, xerostomia, xerophthalmia and dyspnea, which became progressively more marked. There was no evidence of pulmonary, respiratory or renal involvement.

The physical examination revealed arterial blood pressure of 100/70 mmHg; heart rate, 80 beats/min; respiratory rate, 16 breaths/min; body temperature, 36 °C; body weight, 63 kg; prominent second heart sound localized to pulmonary valve; 2/3 jugular distension without inspiratory collapse; mouth opening limitation; facial telangiectasias; generalized skin thickening with a Rodnan skin score of 27/51; and mild Raynaud’s phenomenon.

The laboratory findings were: antinuclear antibodies, 1/1280, with a fine speckled pattern; negative tests for Scl-70, anti-centromere, anti-RO, anti-LA and anti-ribonucleoprotein (RNP) antibodies; and brain natriuretic peptide, 2495 pg/mL. Transthoracic echocardiography revealed global hypokinesia with severely depressed systolic function (SF); left ventricular (LV) ejection fraction, 25%; dilated right cardiac chambers, with depressed right ventricular (RV) SF; severe tricuspid regurgitation; LV with restricted mitral flow. Chest computed tomography showed no evidence of lung parenchyma involvement. Capillaroscopy revealed a pattern of active DSS. Cardiac MRI demonstrated dilation and severe deterioration of LV SF, dilation of left atrium, gadolinium enhancement with a diffuse subendocardial pattern consistent with fibrosis secondary to scleroderma, with extensive myocardial involvement; dilation and severe deterioration of RV SF; mild pericardial effusion; and T2-weighted images without edema. Neither skin biopsy nor other imaging studies (single-photon emission computed tomography [SPECT]) were performed.

The patient was being treated with azathioprine at 150 mg/day, meprednisone at 20 mg/day, nebivolol at 5 mg/day, losartan at 50 mg/day, spironolactone at 50 mg/day, furosemide at 40 mg/day and omeprazole at 20 mg/day.

As the patient failed to respond to this regimen, heart transplantation was performed. At discharge, her immunosuppressive therapy consisted of tacrolimus 3 mg/day, mycophenolate mofetil 2 g/day, meprednisone 20 mg/day and leukovorin 15 mg/day.

Post-transplantation TTE showed preserved RV and LV function, and an ejection fraction of 55%. A biopsy revealed marked replacement fibrosis in large areas of myocardium and endocardium, and in portions with transmural involvement.

Fifteen days after transplantation, the patient experienced cardiopulmonary arrest and failed to respond to resuscitation

maneuvers. The outcome was attributed to humoral immunity-mediated rejection.

Discussion

Early selective cardiac involvement in patients with scleroderma is an uncommon occurrence.

Goetz and Berne coined the term systemic sclerosis in 1945.⁸ Earlier, Heine (1926)⁹ and Weiss and Warren (1943)¹⁰ had described cardiac involvement in this disease.

In 1943, Weiss, Stead and Warren reported 9 cases of patients with cutaneous involvement associated with heart disease.¹¹

A study published in 1976 by Bulkeley et al. of Johns Hopkins Hospital included 52 cases of autopsies in which they found “contraction band necrosis and replacement of the myocardial tissue by patchy fibrosis, with no associated coronary artery disease or pulmonary hypertension”.⁶ A number of reviews indicate an incidence of cardiac manifestations in 15%–35% of the patients with SS.¹²

Domsic et al.¹³ demonstrated that severe cardiac involvement was significantly more common in patients with rapid skin progression. The latter was associated with severe heart disease in 3% of the patients, versus 1% of those with slow progression.

Magnetic resonance imaging was found to have greater sensitivity and specificity for the study of cardiac involvement than TTE. Moreover, MRI is an accurate and reliable technique for the diagnosis of cardiac involvement in SS and for the accurate analysis its mechanisms, including inflammatory, microvascular and fibrotic components. As it is noninvasive, quantitative and highly sensitive, MRI appears to be the method of choice for the determination of the natural history of untreated patients, or for the accurate monitoring of the effects of treatment. Compared with TTE, MRI seems to provide additional information regarding the visualization of myocardial infarction and fibrosis, there being linear late gadolinium enhancement with a subendocardial pattern.⁵

The course of our patient was indolent, but was also atypical of that associated with the underlying disease, with selective cardiac involvement that was resistant to medical treatment, and cardiac transplantation was ultimately required.

Cardiac transplantation is currently considered to be the treatment of choice in end-stage heart failure refractory to medical treatment. Graft rejection is one of the most feared complications. Three types of rejection have been recognized: hyperacute, acute (cellular and humoral) and chronic. Our patient had acute humoral rejection, which can develop days or weeks after transplantation. One of its features is the possibility of rejection episodes with hemodynamic compromise and no evidence of cellular infiltration in the biopsy. Humoral rejection is mediated by antibodies—more than by cells—directed against donor human leukocyte antigens (HLA) or endothelial antigens. It affects 7% of transplant recipients and occurs more frequently in women. It is associated with severe left ventricular dysfunction (47% of the cases) and a higher incidence of chronic rejection.^{14–16}

In an extensive review of the literature, we found only 2 similar cases. One occurred in a 14-year-old girl who had a diagnosis of DSS, with cutaneous and selective cardiac involvement, but that affected no other organs. Like our patient, she tested positive for antinuclear antibodies in the absence of any other antibodies, TTE revealed global hypokinesia and an endomyocardial biopsy disclosed fibrosis. Likewise, despite medical treatment, her course was indolent and she ultimately required heart transplantation. Despite the administration of immunosuppressive therapy, she died 27 months later due to humoral rejection.¹⁷ The other case we found was that of a 36-year-old man with a 3-year history of DSS, but only cardiac and cutaneous involvement. The findings on TTE, MRI and cardiac biopsy were similar to those observed in our

patient. Despite optimal medical treatment, his heart failure progressed rapidly, requiring emergency transplantation. The article mentions that the patient was alive more than 1 year after the intervention.¹⁸

We report this case because of the low prevalence of this mode of presentation of DSS.

Conclusion

Although the case report we present here had a fatal outcome due to graft rejection, the literature includes the report of a successful outcome 1 year after the patient underwent transplantation.

Ethical Disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflicts of Interest

The authors declare they have no conflicts of interest.

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