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Journal of Interdisciplinary Medicine

CASE REPORT

CARDIOLOGY // RHEUMATOLOGY

Limited Cutaneous Scleroderma-Related Pulmonary Arterial Hypertension — a Case Report

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ARTICLE HISTORY

Received: 15 April, 2016
Accepted: 27 May, 2016

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ABSTRACT

Background: Pulmonary hypertension (PH), defined by mean pulmonary arterial pressure (PAPm) ≥25 mm Hg, can lead to increasing pulmonary vascular resistance, which eventually results in right ventricle failure. Scleroderma, as an autoimmune connective tissue disease, is associated with PH as a sub-group according to the 2015 ESC/ERS PH classification. Pulmonary arterial hypertension (PAH) associated with scleroderma (SSc-PAH) can often result in poor prognosis with increased mortality. Early diagnosis and specific treatment of PH can significantly improve the prognosis of these patients. **Case report:** We present the case of a 50 year-old male, with no relevant family history, with a 2-year history of echocardiography-based diagnosis of PH (PAPm 78 mmHg). Physical examination revealed limited hand and forearm areas of non-folding thick skin, vital signs in the normal range and peripheral oxygen saturation of 96%. Severity and risk assessment were performed based on clinical and imaging tests, and hemodynamics. 12-lead rest ECG revealed sinus tachycardia and right bundle branch block, the six-minute walk test confirmed limited exertion capacity, Borg scale 9. Transthoracic echocardiography pointed to dilated right heart cavities and moderate pericardial effusion. Right heart catheterization confirmed the PAH (PAPm: 36 mmHg), and pulmonary CT angiography excluded massive pulmonary embolism. Rheumatologic examination and immune serology identified a scleroderma subset, limited cutaneous sclerosis form (lcSSc) with early onset PH. Combined specific PH drug therapy was initiated, followed by clinical and functional improvement in clinical status, prognosis and life quality. **Conclusions:** In clinical group 1 of PH, the subgroup etiology of PAH associated with connective tissue disease (1.4.1) often goes undiagnosed, mainly due to the diminish of lung involvement symptoms in early CTD stages. Multidisciplinary approach is essential in order to refine the diagnosis and set out the treatment algorithm.

Keywords: pulmonary hypertension, connective tissue disease, diagnosis, specific therapy, multidisciplinarity

INTRODUCTION

Pulmonary hypertension (PH) is a pathophysiological disorder characterized by an increase in the mean pulmonary arterial pressure (PAPm) ≥25 mmHg at rest, as assessed by right heart catheterization (RHC).

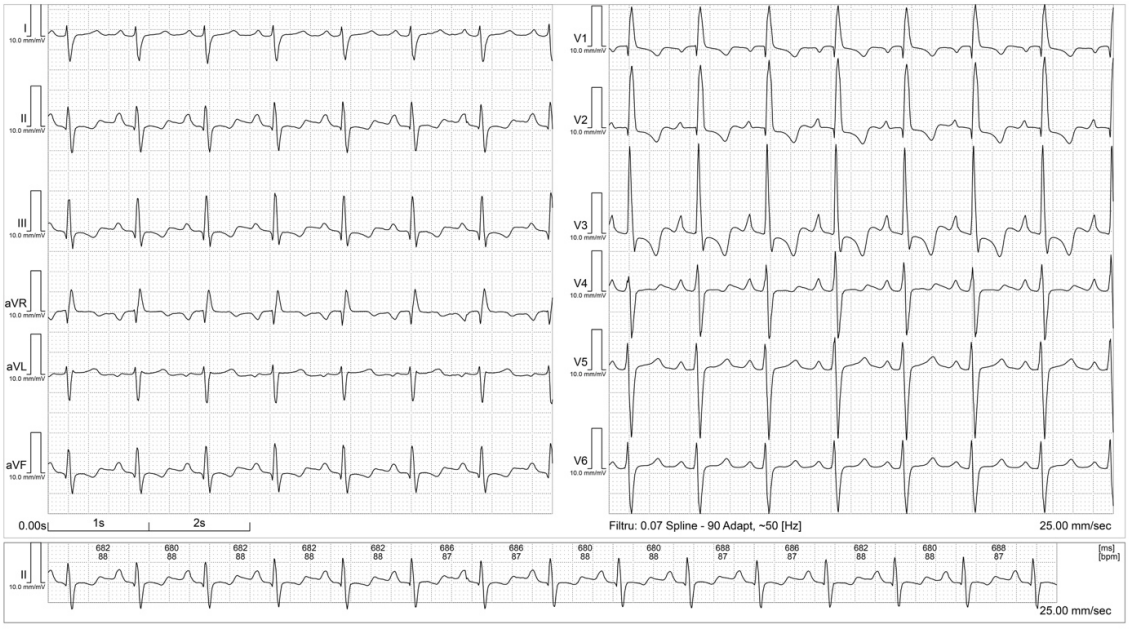


FIGURE 1. Rest ECG recording showing sinus tachycardia and right ventricular overload

This condition can lead to sustained and progressive increase in pulmonary vascular resistance, which eventually may result in right ventricle (RV) failure. Diagnosed late and untreated, this life-threatening condition has a poor prognosis. Treatment of the specific causes can improve the prognosis and assure therapeutic success.[1]

The comprehensive clinical classification of PH according to the 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension, recognize five main groups of PH, pulmonary arterial hypertension (PAH) representing group I. This is characterized hemodynamically by the presence of pre-capillary PH (PAPm ≥25 mmHg, PAWP ≤15 mmHg) and pulmonary vascular resistance >3 Wood units.

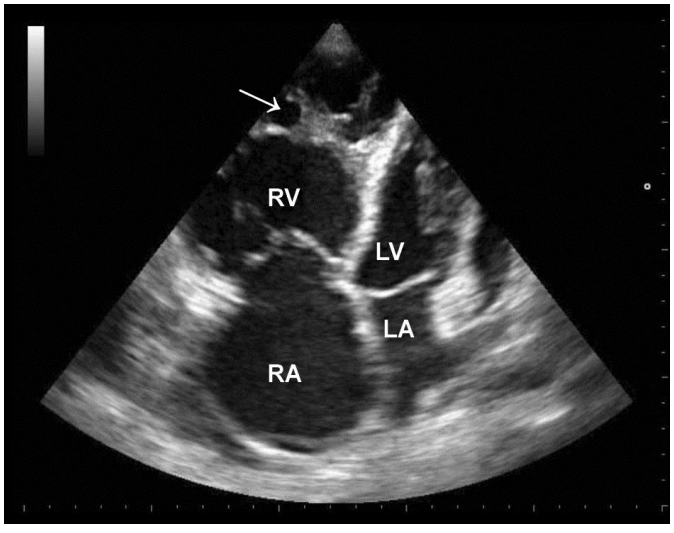


FIGURE 2. Apical 4 chambers view. Dilated right heart cavities, right ventricle trabeculae are seen (arrow)

Connective tissue diseases (CTD), as a distinctive group of disorders, lead to PAH, in addition to multiple complications. This specific entity is identified as subgroup 1.4.1 in the most recent clasification.[3] Systemic scleroderma (SSc) is associated with pre-capillary PH in about 5 to 12% of patients already diagnosed with connective tissue diseases.[6]

In the group of autoimmune CTD, systemic scleroderma is characterized by progressive fibrosis of the skin and vasculopathy with multiple visceral damage, including the lungs. Scleroderma prevalence is low, but it has high morbidity and mortality.

Pulmonary hypertension associated with scleroderma (SSc-PAH) can often result in poor prognosis with increased mortality. Not only diffuse cutaneous, but also limited cutaneous forms of scleroderma are at risk for cardiac involvement and SSc-PAH.

Screening for the presence of scleroderma in PH diagnosed patients should be performed, as earlier diagnosis and treatment can result in a better prognosis.[8]

CASE PRESENTATION

We present the case of a 50 year-old man, referred to a PH referral center presenting exertional dyspnea, fatigue, episodes of syncope and mild peripheral edema.

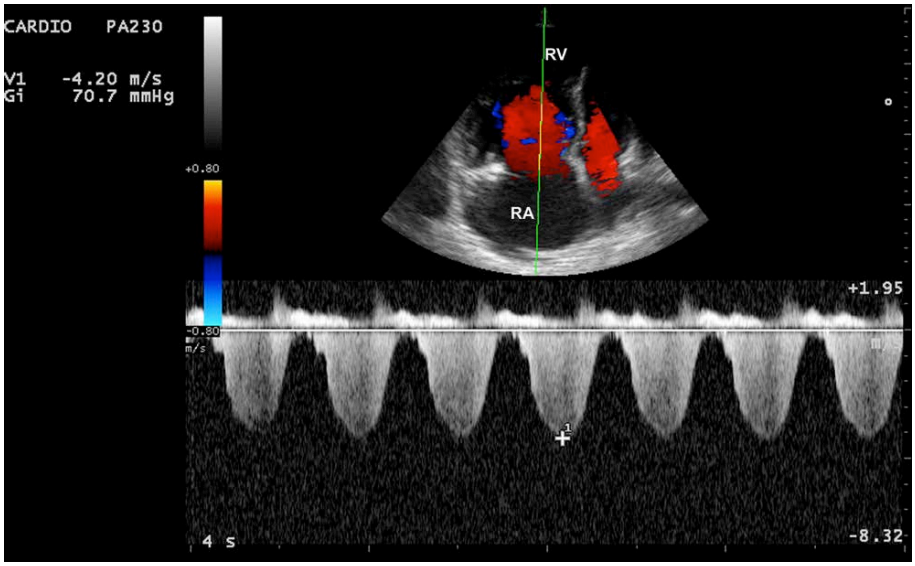


FIGURE 3. Severe tricuspid regurgitation (70.7 mmHg)

Family history was negative for pulmonary or heart diseases with significance in the patient's present status. From previous medical records the patient had a 2-year history of PH diagnosis based on echocardiographic data (mean systolic pulmonary artery pressure of 78 mmHg).

The patient was also an ex-smoker, with previous moderate alcohol consumption.

On admission, physical examination revealed normal BMI: 20.7 kg/m^2, afebrile status, apparently no respiratory or infectious diseases at the time of examination and no signs of any neurological disorder. Skin examination revealed areas of thick skin, almost impossible to fold, localized on both hands and also small areas on both forearms. Lymph node examination did not show any significant findings. Vital signs were within normal range: BP was 115/70 mm Hg, heart rate 116/min, peripheral oxygen saturation assessed by pulse oximetry 96% during rest, without oxygen supply. Cardiac auscultation revealed mitral systolic murmur, II/6 degree in intensity, which radiated posteriorly and to the left axilla. An increased enlarged liver (about 18 cm), slightly tender to palpation was noticed during abdominal examination.

Based on previous echocardiographic probability of pulmonary hypertension in a symptomatic patient with a clinical suspicion of PH, further investigations were scheduled in order to confirm and to identify the clinical classification of pulmonary hypertension.

Evaluation of severity and risk assessment of the patient was performed based on clinical parameters, routine and additional tests, imaging and hemodynamics.[3]

Twelve-lead rest ECG detected sinus tachycardia (Figure 1) at an average heart rate of 112 bpm, right ventricular overload expressed by the presence of pulmonary P wave, right QRS axis deviation, qR aspect in V1, R wave in V2, right bundle branch block.

Routine blood tests revealed initially elevated gamma GT levels (183 U/l) which decreased under right heart failure treatment to 162 U/l; NT-pro BNP plasma levels 3,215.00 pg/ml.

Six-minute walk test (6MWT) confirmed dyspnea on exertion, with a decrease in peripheral oxygen saturation from 96% at rest to 85% and an increase in heart rate from

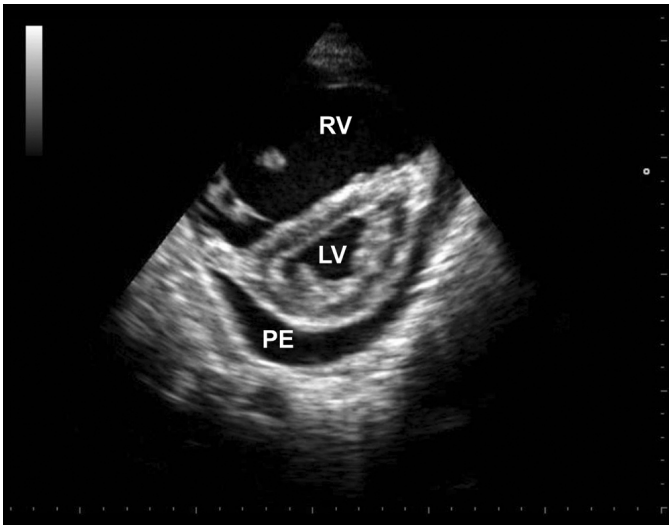
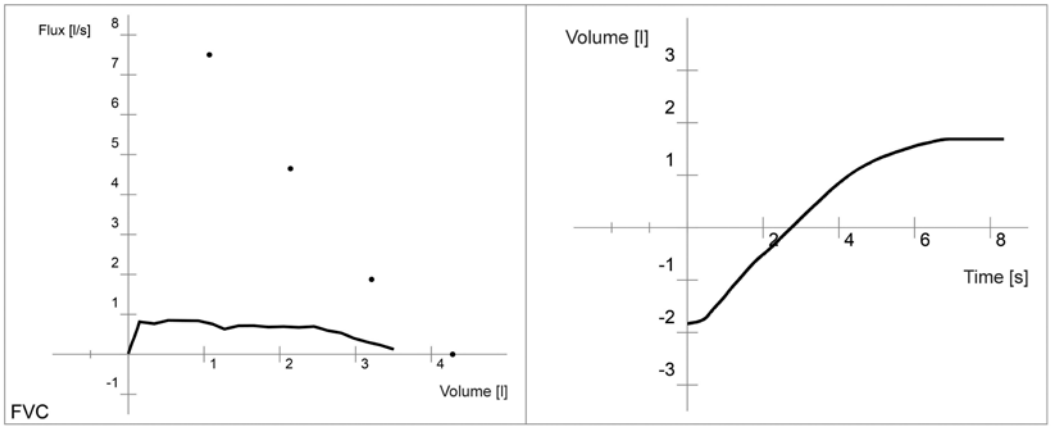


FIGURE 4. Two-dimensional echocardiogram of circumferential pericardial effusion. Right ventricle is enlargerd and interventricular septum is flattened.



Parameter	Unit	Predicted	Pre test	% Predict.
FVC	l	4.28	3.52	82.24
FEV1	l	3.48	0.91	26.15
PEF	l/s	8.62	0.97	11.25
FEV1/FVC	%	78.39	25.84	32.96
MMEF	l/s	3.94	0.70	17.77
MEF75	l/s	7.50	0.83	11.07
MEF50	l/s	4.65	0.71	15.27
MEF25	l/s	1.88	0.61	32.45
Aex	l^2/s	–	2.24	–

FIGURE 5. Rest test spirometry – mild restrictive respiratory dysfunction

FVC – Forced Vital Capacity; FEV1 – Forced Expiratory Volume in 1 second; PEF – Peak Expiratory Flow; FEV1/FVC – Forced Expiratory Volume in 1 second/Forced Vital Capacity; MMEF – Maximum Mid-Expiratory Flow; MEF75 – Maximum Expiratory Flow 75%; MEF50 – Maximum Expiratory Flow 50%; MEF25 – Maximum Expiratory Flow 25%; Aex – Lung age

110 bpm to 120 bpm. A walk test on 220 meters was performed in 6 minutes, Borg scale 9 at the end of the 6MWT.

Transthoracic echocardiography showed dilated right heart cavities, hypokinetic right ventricle, right ventricular hypertrophy, minor mitral and pulmonary regurgitation, moderate to severe tricuspid regurgitation, dilated pulmonary artery (both trunk and main branches), with a mildly decreased ejection fraction (50%); a small to moderate pericardial effusion (PE) was also noticed.

Peripheral venous Doppler ultrasound examination was within the normal limits and respiratory functional test (spirometry) showed mild restrictive respiratory dysfunction.

Chest X-Ray revealed central pulmonary arterial dilatation; no right atrium or right ventricle enlargement was observed.

After classification as intermediate-to-high risk of PH, the evaluation continued with the right heart catheterization (RHC) as a definitive diagnosis tool for the identification of the more common clinical groups of PH group 2 (LHD) and group 3 (lung diseases), distinguishing group 4 (CTEPH) and state the diagnosis for further recognition of the different types in group 1 (PAH).

RHC confirmed the diagnosis of pre-capillary PAH with a mean pulmonary artery pressure of 36 mm Hg (69/22/36 mmHg) and an indexed pulmonary vascular resistance of 15.01 HRUI.

CT pulmonary angiography showed no evidence of pulmonary thromboembolism, but confirmed both right heart and pulmonary artery morphological changes.

Immune serology was tested for the accurate etiology of different forms with similar clinical manifestation of pulmonary arterial hypertension (group 1). The results showed positive IgE (559.4 UI/l), anti-nuclear antibodies (ANA), IgG cardiolipin antibodies (26.4 UGPL/ml), borderline increased of SCL-70 levels and increased levels of U3-RNP (anti-fibrillar) antibodies.

The first therapeutic decision, along with the initial approach that included general measures and supportive therapy (diuretics), was addressed to specific therapy for pulmonary arterial hypertension.

TABLE 1. Haemodynamic assessment; data from RHC

Resistance	HRU	HRUI
PVR	8.73	15.01
TPVR	10.14	17.43
SVR	25.62	44.07
TSVR	26.19	45.04
PVR/SVR	0.34	
TPVR/TSVR	0.39	

TABLE 2. Haemodynamic assessment; determination of flows using the Fick method

Flows (Fick method)	
Cardiac output	3.55 l/min
Cardiac index	2.6 l/min/m^2
Systemic output (Qs)	3.55 l/min
Indexed systemic output (Qsi)	2.06 l/min
Pulmonary output (Qp)	3.55 l/min
Indexed pulmonary output (Qpi)	2.06 l/min
Qp/Qs ratio	1

Initial drug monotherapy with initiation of oral active dual endothelin receptor type A and B antagonist (ERA) Bosentan 125 mg/daily, with rather good clinical response, was extended to sequential drug combination therapy with phosphodiesterase type 5 inhibitors, 40 mg Sildenafil daily.

Considering the fact that PAH was associated with limited cutaneous scleroderma, we decided to combine the specific therapies for both diseases, in the lowest doses resulting in a maximum effect. Therefore, the patient is currently under treatment with 10 mg methotrexate/week to improve prognosis and life expectancy. Follow-up of immunomodulatory and specific antifibrotic therapy for scleroderma diminished the skin lesion progression with good drug tolerance. The patient's clinical evolution in the following 6 months from the start of treatment will define the adjusting of methotrexate dose in the treatment of scleroderma.

According to current guidelines regarding the evaluation of severity and risk assessment in PAH, the patient was assessed at three months: no progression of symptoms or syncope, WHO functional class I/II, 6MWT: 580 m, Borg scale 2/3 (form 9), transthoracic echocardiography with a decrease of systolic pulmonary arterial pressure from 85 to 50 mmHg, with intermediate risk (RA area 25 cm^2, minimal pericardial effusion and NT-proBP values of 2,123.00 pg/ml).

DISCUSSION

Concerning the etiology of PAH, connective tissue disease was suspected based on the patient's history (smoking, alcohol consumption), clinical presentation (fatigue, dyspnea), clinical appearance (skin modifications) and pericardial effusion presence (transthoracic echocardiography, CT pulmonary angiography).

Data from specific literature infer that when compared to idiopathic PAH (IPAH), patients with SSc-PAH are more frequently females, older and present more advanced stages of illness.

Immune serology pointed initially to undifferentiated connective tissue disease or scleroderma on its onset, as SCL-70 and U3-RNP (anti-fibrillarin) antibodies were borderline at first dosage. Laboratory findings pointed also to high levels of IgE (559.4 UI/l), anti-nuclear antibodies (ANA) positive, Ig G cardiolipin antibodies (26.4 UGPL/ml) positive. SCL-70 and U3-RNP (anti-fibrillarin) antibodies were elevated on repeated dosage, after six months.

The diagnosis of scleroderma was established using 2013 ACR/EULAR Classification Criteria for Scleroderma. Based on the findings above, the diagnosis score for the patient was 14 points (skin thickening of the fingers of both hands, extending proximally to the metacarpal joints — the most important and sufficient criterion, PAH present, borderline positive SCL-70 and increased anti-fibrillarin (U3-RNP) antibodies).

Skin modifications of the hands were the main criterion for scleroderma diagnosis. It is most likely that the connective tissue disease was diagnosed at its onset, as the specific antibodies have turned positive in a six months period. Other connective tissue diseases were discussed in the case of this patient, mainly systemic lupus erythematosus (SLE), rheumatoid arthritis and mixed connective tissue disease (MCTD). The differential diagnosis of scleroderma was finally made on immune serology basis, as ADNdc and Sm antibodies — specific for SLE and/or MCTD, cyclic citrullinated peptide (CCP) antibodies — specific for RA and U1-RNP antibodies — specific for MCTD were absent or negative.

The particularity of the case lies in the fact that the patient presented with symptoms of non-specific PH, mainly related to progressive right ventricular (RV) dysfunction, present since the onset of scleroderma. In the literature, 60% of SSc-related deaths are associated to the direct pulmonary involvement of SSc, determining interstitial lung disease and PH.

Furthermore, PH is more common in a subset of limited cutaneous sclerosis form (lcSSc) when compared to diffuse disease.

CONCLUSIONS

In pulmonary hypertension, clinical group 1 (PAH) the etiology of subgroup PAH, associated with connective tissue disease (1.4.1) often goes undiagnosed, mainly due to the diminish of lung involvement symptoms in early CTD stages.

A multidisciplinary approach including general practitioners, pneumologists, cardiologists and rheumatologists in the evaluation of PH in these patients is essential in order to refine the diagnosis and set out the treatment algorithm.

CONSENT

Written informed consent was obtained from the patient for the publication of this case report. A copy of the consent is available at request.

CONFLICT OF INTEREST

Ioan Ţilea, Codruța Maria Gal, and Andreea Varga received scientific support from Pfizer and Actelion.

ABBREVIATIONS

RV	Right ventricle
SSC	Systemic Scleroderma
CTD	Connective tissue disease
PH	Pulmonary hypertension
PAH	Pulmonary arterial hypertension
MCTD	Mixed connective tissue disease
SLE	Systemic lupus erythematosus
RA	Right atrium
LA	Left atrium
LV	Left ventricle
RHC	Right heart catheterization
PAWP	Pulmonary artery wedge pressure
BMI	Body mass index
BP	Blood pressure
PE	Pericardial effusion
CTEPH	Chronic thromboembolic pulmonary hypertension
LHD	Left heart disease
PVR	Pulmonary vascular resistance
TPVR	Total pulmonary vascular resistance
SVR	Systemic vascular resistance
TSVR	Total systemic vascular resistance
WHO	World Health Organization

REFERENCES

1. Hoeper MM, Bogaard HJ, Condliffe R, et al. Definitions and diagnosis of pulmonary hypertension. *J Am Coll Cardiol*. 2013;62(Suppl):D42-D50.
2. Nader Kamangar et al, Secondary Pulmonary Hypertension, http://emedicine.medscape.com/article/303098-overview#showall
3. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *European Heart Journal*. 2016;37,67-119. doi:10.1093/eurheartj/ehv317.
4. Khanna D, Gladue H, Channick R, et al. Recommendations for screeningand detection of connective tissue disease-associated pulmonary arterial hypertension. *Arthritis Rheum*. 2013;65:3194-3201.
5. Hajj-ali, RA (June 2013). Systemic Sclerosis. Merck Manual Professional. Merck Sharp & Dohme Corp.
6. Vandecasteele EH, De Pauw M, Brusselle G, et al. The heart and pulmonary arterial hypertension in systemic sclerosis. *Acta Clin Belg*. 2016;5:1-18.
7. Hachulla E, Gressin V, Guillevin L, et al. Early detection of pulmonary arterial hypertension in systemic sclerosis: a French nationwide prospective multicenter study. *Arthritis Rheum*. 2005;52:3792-3800.
8. Clements PJ, Tan M, McLaughlin VV, et al. The pulmonary arterial hypertension quality enhancement research initiative: comparison of patients with idiopathic PAH to patients with systemic sclerosis-associated PAH. *Ann Rheum Dis*. 2012;71:249-252.
9. Van der Hogen, et al. 2013 ACR/EULAR Classification Criteria for Scleroderma, Arthritis and Rheumatism. 2013,65:2737-2747.
10. Kavanaugh A, Tomar R, Reveille J, et al. Guidelines for clinical use of the antinuclear antibody test and tests for specific autoantibodies to nuclear antigens. American College of Pathologists. *Arch Pathol Lab Med*. 2000;124:71.
11. Russo K, Hoch S, Dima C, et al. Circulating anticentromere CENP-A and CENP-B antibodies in patients with diffuse and limited systemic sclerosis, systemic lupus erythematosus, and rheumatoid arthritis. *J Rheumatol*. 2000;27:142.
12. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972–2002. *Ann Rheum Dis*. 2007; 66:940-944.
13. Gabrielli A, Avvedimento EV, Krieg T. Scleroderma. *N Engl J Med*. 2009;360:1989-2003.