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【 CASE REPORT 】

Premature Onset Aortic Stenosis in Systemic Sclerosis: A Report of a Series of Cases

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Abstract:

Although cardiovascular involvement is a well-known complication correlated with a poor prognosis in patients with systemic sclerosis, there are few reports on valvular heart disease. Forty patients with systemic sclerosis were retrospectively analyzed. Valvular heart disease was found in six patients, five of whom had severe tri-leaflet aortic stenosis. Three of these 5 patients were ≤71 years old. Two frail elderly patients who underwent transcatheter aortic valve replacement died within two years.

Premature-onset aortic stenosis is not uncommon in patients with systemic sclerosis. When considering mechanical intervention, the evaluation of frailty is important.

Key words: aging society, clinical frailty scale, elderly patient, premature onset aortic stenosis, systemic sclerosis, transcatheter aortic valve replacement

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Introduction

Systemic sclerosis (SSc) is a multisystem disease characterized by immune system activation with the presence of SSc-specific autoantibodies, systemic microvascular and macrovascular abnormalities, and disturbances in the fibroblast function, leading to fibrosis in multiple organs (1, 2). Although cardiovascular involvement such as myocardial fibrosis, microvascular ischemia, ventricular dysfunction and heart failure, coronary artery disease, conduction disturbances, arrhythmias, pericardial disease, and pulmonary hypertension, are well-known complications correlated with a poor prognosis in patients with SSc (3-9), there are few reports on valvular heart disease, particularly aortic stenosis (AS) (10, 11). However, given the relatively long life expectancy of the general population as well as improvements in the survival based on recent therapeutic advances among SSc patients, it may not be uncommon for SSc patients to have degenerative AS.

We herein report five SSc patients complicated by severe degenerative AS, the progression of which might have been prematurely accelerated by the underlying chronic inflammatory burden.

The Case Identification And Evaluation

Between January 2008 and January 2018, 46 consecutive patients with SSc who were admitted to Chikamori hospital were retrospectively evaluated. The diagnosis of SSc was based on the American College of Rheumatology (ACR) criteria for SSc (1980) (1) and the 2013 classification criteria for SSc by the ACR/European League against Rheumatism (EULAR) collaborative initiative (12). Six patients were excluded because they did not undergo an echocardiographic examination and were not considered suitable for the analysis of valvular heart disease. Therefore, 40 patients with SSc [33 women and 7 men; mean age 75.1±14.1 (range: 27-99) years old] were included in the analysis for valvular heart

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Table 1. Clinical Characteristics of the Five AS Patients.

Case	Age at Dx	Sex	SSc type	Auto-antibodies	CFS grading at Dx	NYHA class at Dx	Management	F/U (Months)	Current status (Cause of death)
1	70	F	LS	ANA anti-centromere	3	II	AVR	81	Re-AVR/Alive
2	71	F	LS	ANA	5	III	TAVR	71	Deceased (IP/ARDS)
3	71	F	DS	ANA anti-Scl-70	6	III	TAVR	14	Deceased (Stroke)
4	77	F	LS	ANA	6	II	Medical	27	Alive
5	77	F	LS	ANA anti-centromere	3	III	Medical	32	Deceased (Sudden death)

ANA: anti-nuclear antibody, ARDS: acute respiratory distress syndrome, AS: aortic stenosis, AVR: aortic valve replacement, CFS: clinical frailty scale, DS: diffuse subtype, Dx: diagnosis, F: female, F/U: follow-up, IP: interstitial pneumonia, LS: limited subtype, NYHA: New York Heart Association, Scl: scleroderma, SSc: systemic sclerosis, TAVR: transcatheter aortic valve replacement

Table 2. Laboratory Data of the Five AS Patients.

Case		1	2	3	4	5
BNP	(pg/mL)	493	115	2,476	127	121
WBC	(/μL)	5,900	9,800	19,100	3,500	2,700
RBC	($\times10^4$/μL)	396	467	356	292	377
Hb	(g/dL)	11.8	13.4	10.6	9.5	11.5
Plt	($\times10^4$/μL)	17.9	26.5	33.4	22.3	11.5
CRP	(mg/dL)	0.5	1.1	1.8	0.5	3.6
CPK	(IU/L)	78	64	88	67	38
LDH	(IU/L)	323	265	280	215	303
GOT	(IU/L)	25	35	30	42	32
GPT	(IU/L)	16	25	19	30	15
ALP	(IU/L)	234	355	125	1,145	434
BUN	(mg/dL)	15.4	20.8	17.9	16.2	32.0
Crn	(mg/dL)	0.8	0.6	0.9	0.5	1.8
Na	(mEq/L)	142	141	141	139	130
K	(mEq/L)	5.0	4.0	3.6	4.2	3.3
Cl	(mEq/L)	110	103	103	107	96
T-chol	(mg/dL)	202	157	165	250	195
ALB	(g/dL)	4.0	4.2	3.6	3.5	2.4

ALB: albumin, ALP: alkaline phosphatase, BNP: B-type natriuretic peptide, BUN: blood urea nitrogen, Cl: chloride, CPK: creatine phosphokinase, Crn: creatinine, CRP: C-reactive protein, GOT: glutamate-oxaloacetate transaminase, GPT: glutamate-pyruvate transaminase, Hb: hemoglobin, K: kalium, LDH: lactate dehydrogenase, Na: natrium, Plt: platelet, RBC: red blood cell, T-chol: total cholesterol, WBC: white blood cell

disease. The subtype of SSc was identified as diffuse SSc in 8 patients and limited SSc in 32 patients. The follow-up period was 37±36 months.

The evaluation of patients included a chart review of their medical history and a clinical examination, 12-lead electrocardiography, chest radiography, and blood test for autoantibodies. M-mode, two-dimensional, and Doppler echocardiography was also performed. The left ventricular end-diastolic diameter, end-systolic diameter, and left atrial diameter were measured based on M-mode and two-dimensional images obtained from parasternal long-axis views. The magnitude of left ventricular hypertrophy was assessed in the parasternal long-axis and short-axis planes just below the mitral valve level. The ejection fraction was determined from the parasternal long-axis plane and two-and four-chamber views. The aortic valve gradient was calculated from continuous-wave Doppler using the simplified Bernoulli equation.

Case Reports

Six patients were found to have severe valvular heart disease. Tri-leaflet degenerative severe AS was found in five patients. One patient had rheumatic mitral stenosis.

The clinical characteristics and laboratory data of the five patients with severe AS are summarized in Tables 1 and 2. The age at the diagnosis of the patients with severe AS ranged from 70 to 77 years old. Three of the 5 patients were ≤71 years old. All patients were women. The mean New York Heart Association (NYHA) functional class was 2.6. The semiquantitative Clinical Frailty Scale (CFS) was used to evaluate patients' frailty (13, 14). The CFS ranges from 1 (very fit) to 9 (terminally ill) and is a simple tool for assessing patients' frailty and predicitng mortality in elderly patients. The CFS was found to be 3 (non-frail) in two patients (cases 1 and 5), 5 (mildly frail) in one patient (case 2), and 6 (moderately frail) in two patients (cases 3 and 4) (Table 1). The echocardiographic findings, including left ventricular systolic and diastolic function, left ventricular mass, and other Doppler hemodynamic indices, are presented in Table 3. All patients had a left ventricular ejection fraction of >65%. Regarding aortic valve characteristics, all patients had tri-leaflet degenerative severe AS with significant calcification of the aortic valve. The mean aortic valve area was 0.69 cm^2.

Cases with mechanical AS intervention

Three patients had a clinical diagnosis of severe AS at ≤71 years old. All patients had symptoms of heart failure including one case (case 1) of NYHA functional class II and

Table 3. Echocardiographic Findings of the Five AS Patients.

Case		1	2	3	4	5
LVDd	(mm)	45	35	45	35	39
LVDs	(mm)	26	22	28	22	24
LVEF	(%)	73	68	67	67	69
IVS	(mm)	10	11	13	9	12
PW	(mm)	10	11	13	8	11
LA	(mm)	46	31	41	33	30
Ao	(mm)	34	32	36	31	28
LVM	(g)	115	81	253	82	130
LVMi	(g/m^2)	84	67	204	75	92
SVi	(mL/m^2)	51.0	49.3	49.6	44.3	38.6
AoV : Vmax	(m/s)	3.8	3.7	5.2	4.7	3.9
mPG	(mmHg)	37	31	54	41	32
AVA	(cm^2)	0.71	0.91	0.54	0.52	0.77
AVAi	(cm^2/m^2)	0.51	0.75	0.43	0.48	0.53
MV : E	(cm/s)	110	51	78	116	71
A	(cm/s)	129	101	134	211	68
E/A		0.85	0.51	0.58	0.55	1.04
DcT	(ms)	308	354	346	363	250
Pericardial effusion		Trace	Trace	Massive	Trace	Large

A: A wave, Ao: aortic root, AoV: aortic valve, AVA: aortic valve area, AVAi: aortic valve area index, DcT: deceleration time, E: E wave, E/A: E/A ratio, IVS: interventricular septal thickness, LA: left atrial dimension, LVDd: left ventricular diastolic dimension, LVDs: left ventricular systolic dimension, LVEF: left ventricular ejection fraction, LVM: left ventricular mass, LVMi: left ventricular mass index, mPG: mean pressure gradient, MV: mitral valve, PW: posterior wall thickness, SVi: stroke volume index, Vmax: maximum flow velocity

two cases (cases 2 and 3) of NYHA functional class III. Aside from premature-onset degenerative tri-leaflet AS, several cardiovascular comorbidities of SSc were found in two of the three patients. Significant stenosis of the left anterior descending coronary artery was found in one patient (case 3) in whom percutaneous coronary intervention was successfully performed. Peripheral artery disease was found in one patient (case 1) in whom endovascular treatment was performed. Regarding conduction disturbance and arrhythmia, complete heart bock was found in one patient (case 3) in whom a permanent pacemaker was implanted. Case 3 also had massive pericardial effusion and underwent pericardial window surgery.

With respect to the management of severe AS, one patient (case 1) had surgical aortic valve replacement (AVR), and two patients (cases 2 and 3) underwent transcatheter aortic valve replacement (TAVR). Of the two frail elderly patients who received TAVR, case 2 died of acute respiratory failure within two years, and case 3 died of stroke without functional improvement within one year. In addition to apparent frailty, both patients continued to have heart failure symptoms with left ventricular diastolic dysfunction after TAVR.

Cases with medical management

Two patients had a clinical diagnosis of severe AS at 77 years old. These two patients were symptomatic: case 4 had NYHA functional class II, and case 5 had NYHA functional class III. Regarding other cardiovascular involvement of SSc, case 4 was found to have single-vessel coronary artery disease. Atrial fibrillation was found in case 5, which also had marked pericardial effusion and underwent thoracoscopic pericardial fenestration.

With respect to the management of severe AS, neither patient (cases 4 and 5) underwent mechanical AS intervention and were instead managed medically. One patient (case 5) died suddenly 32 months after the diagnosis of severe AS.

Discussion

Cardiovascular involvement is common in SSc, which is known as scleroderma heart disease (3). However, cardiovascular manifestations usually remain subclinical. When clinically evident, cardiovascular involvement of SSc is often associated with a poor prognosis (4-6). Valvular heart disease is not considered a typical manifestation of SSc. In particular, information on aortic valve involvement has been very limited (10, 11).

However, the present study indicated that severe degenerative AS was not uncommon, with 5 of the 40 SSc patients showing degenerative severe AS. Although the premature progression of AS is usually seen in patients with bicuspid aortic valve, all five of our patients had tri-leaflet severe AS. It is possible that degenerative AS has been underdiagnosed in SSc patients, since AS has a prolonged course with in-

sidious subclinical progression until classic symptoms such as chest pain, heart failure and syncope, develop (15). In addition, the female predominance of SSc patients may make the correct diagnosis of AS difficult, as women frequently have low-flow, low-gradient, severe AS. These background factors may delay appropriate referral to a cardiologist.

Because of the extended life expectancy in the general population in developed countries, we have recently been witnessing significant increases in the incidence of aging-related degenerative valvular heart disease, such as AS. The result of the present study of premature-onset, degenerative tri-leaflet AS in SSc patients may be due to an improved survival based on advances in therapy for SSc patients together with a prolonged life expectancy in the general population.

Our five patients with degenerative tri-leaflet AS ranged in age from 70 to 77 years old. Three patients were ≤71 years of age, which was much younger than the average age of degenerative AS in the general population (16, 17). The remaining two patients who were 77 years old at the diagnosis also were considered to have developed severe degenerative AS at a relatively early age compared to the average age of AS in the general population.

Hemodynamically significant changes in the aortic valve may begin several years before the diagnosis of AS. Systemic sclerosis is a chronic inflammatory disorder and an underlying inflammatory burden may play a part in accelerating the progression and causing the premature onset of degenerative tri-leaflet AS in SSc patients.

Valvular heart disease in patients with many connective tissue diseases is not uncommon. For example, the population with rheumatoid arthritis has a higher incidence of valvular heart disease than the general population (18), and AS is particularly common in elderly patients with rheumatoid arthritis (19). Recent studies have indicated that inflammatory cytokines, such as tumor necrosis factor, involved in rheumatoid arthritis may lead to inflammation and premature disease of the heart valves (20). It is therefore possible that activation of the inflammatory cascade via tumor necrosis factor may accelerate the progression of valvular heart disease including AS.

The premature progression of AS has also been reported in patients with other connective tissue disease, such as systemic lupus erythematosus and antiphospholipid syndrome (21, 22). In a recent meta-analysis, a three-fold increased risk for any valve lesion was demonstrated in patients with systemic lupus erythematosus and antiphospholipid antibodies compared with those without antiphospholipid antibodies, and inflammatory mechanism was again suspected to be responsible for the premature progression of valvular heart disease (23). We believe that it will become important to anticipate valvular involvement, particularly the involvement of degenerative severe AS, in the management of elderly SSc patients.

In terms of the treatment of severe AS in elderly patients with SSc in whom surgical AVR is considered to carry a high risk because of their comorbidities such as frailty and pulmonary hypertension, as well as anti-inflammatory medications, it is reasonable to consider the application of TAVR. There are potential advantages with TAVR over surgical AVR in elderly SSc patients (24, 25). However, it is important to understand the technical risk of vascular complications in these elderly patients, who are predominantly women with smaller-caliber arteries, a small annular size, and low coronary ostial height. It is also very important to be aware of the critical roles of frailty and various medical comorbidities, since these are the important factors that can predict the futility of TAVR, defined as the combination of death and/or the absence of functional improvement during follow-up (14, 26-30). Most elderly SSc patients with severe AS are likely frail, elderly women. The indication of TAVR should therefore be assessed with caution in these patients.

The authors state that they have no Conflict of Interest (COI).

References

1. Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Arthritis Rheum **23**: 581-590, 1980.
2. Hudson M, Fritzler MJ. Diagnostic criteria of systemic sclerosis. J Autoimmun **48-49**: 38-41, 2014.
3. Janosik DL, Osborn TG, Moore TL, et al. Heart disease in systemic sclerosis. Semin Arthritis Rheum **19**: 191-200, 1989.
4. Ioannidis JPA, Vlachoyiannopoulos PG, Haidich A-B, et al. Mortality in systemic in systemic sclerosis: an international meta-analysis of individual patient data. Am J Med **118**: 2-10, 2005.
5. Kahan A, Coghlan G, McLaughlin V. Cardiac complication of systemic sclerosis. Rheumatology **48**: iii45-iii48, 2009.
6. Rubio-Rivas M, Royo C, Sineón CP, et al. Mortality and survival in systemic sclerosis: systematic review and meta-analysis. Semin Arthritis Rheum **44**: 208-219, 2014.
7. Roman MJ, Salmon JE. Cardiovascular manifestations of rheumatologic disease. Circulation **116**: 2346-2355, 2007.
8. Champion HC. The heart in scleroderma. Rheum Dis Clin North Am **34**: 181-190, 2008.
9. Avińa-Zubieta JA, Man A, Yurkovich M, et al. Early cardiovascular disease after the diagnosis of systemic sclerosis. Am J Med **129**: 324-331, 2016.
10. Sponga S, Basso C, Ruffatti A, Gerosa G. Systemic sclerosis and aortic valve stenosis: therapeutic implications in two cases of aortic valve replacement. J Cardiovasc Med **10**: 560-562, 2009.
11. Bernelli C, Chieffo A, Giustino G, et al. Preliminary outcomes after transcatheter aortic valve implantation in patients with systemic sclerosis. EuroIntervention **10**: 1464-1467, 2015.
12. van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. Arthritis Rheum **65**: 2737-2747, 2013.
13. Rockwood K, Song X, MacKinght C, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ **173**: 489-495, 2005.
14. Shimura T, Yamamoto M, Kano S, et al. Impact of the clinical frailty scale on outcomes after transcatheter aortic valve replacement. Circulation **135**: 2013-2024, 2017.
15. Ross J Jr, Braunwald E. Aortic stenosis. Circulation **37/38** (Suppl): V-61-V-67, 1968.

16. Stewart BF, Siscovick D, Lind BK, et al. Clinical factors associated with calcific aortic valve disease. J Am Coll Cardiol **29**: 630-634, 1997.

17. Eveborn GW, Schirmer H, Heggelund G, et al. The evoling epidemiology of valvular aortic stenosis. Tromso study. Heart **99**: 396-400, 2013.

18. Kitas G, Banks MJ, Bacon PA. Cardiac involvement in rheumatoid disease. Clin Med (Lond) **1**: 18-21, 2001.

19. Bois JP, Crowson CS, Khullar T, Achenbach SJ, Krause ML, Mankad R. Progression rate of severity of aortic stenosis in patients with rheumatoid arthritis. Echocardiography **34**: 1410-1416, 2017.

20. Lacey D, Hickey P, Arhatari BD, et al. Spontaneous retrotransposon insertion into *TNF* 3′UTR causes heart valve disease and chronic polyarthritis. Proc Natl Acad Sci U S A **112**: 9698-9703, 2015.

21. Nihoyannopoulos P, Gomez PM, Joshi J, Loizou S, Walport MJ, Oakley CM. Cardiac abnormalities in systemic lupus erythematosus. Association with raised anticardiolipin antibodies. Circulation **82**: 369-375, 1990.

22. Krupa J, Chiam PTL, Chua YL, Ewe SH. Feasibility of transcatheter aortic valve implantation in systemic lupus erythematosus associated non-calcific aortic stenosis. Eur Heart J **35**: 1624, 2014.

23. Zuily S, Regnault V, Selton-Suty C, et al. Increased risk for heart valve disease associated with antiphospholipid antibodies in patients with systemic lupus erythematosus: meta-analysis of echocardiographic studies. Circulation **124**: 215-224, 2011.

24. Leon MB, Smith CR, Mack M, et al.; PARTNER Trial Investigators. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med **363**: 1597-1607, 2010.

25. Smith CR, Leon MB, Mack MJ, et al.; PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med **364**: 2187-2198, 2011.

26. Fried LP, Tangen CM, Walston J, et al.; Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci **56**: M146-M156, 2001.

27. Green P, Woglom AE, Genereux P, et al. The impact of frailty status on survival after transcatheter aortic valve replacement in older adults with severe aortic stenosis: a single-center experience. JACC Cardiovasc Interv **5**: 974-981, 2012.

28. Puls M, Sobisiak B, Bleckmann A, et al. Impact of frailty on short-and long-term morbidity and mortality after transcatheter aortic valve implantation: risk assessment by Katz Index of activities of daily living. EuroIntervention **2012;10**: 609-619, 2012.

29. Green P, Arnold SV, Cohen DJ, et al. Relation of frailty to outcomes after transcatheter aortic valve replacement (from PARTNER Trial). Am J Cardiol **116**: 264-269, 2015.

30. Puri R, Iung B, Cohen DV, Rodés-Cabau J. TAVI or no TAVI: identifying patients unlikely to benefit from transcatheter aortic valve implantation. Eur Heart J **37**: 2217-2225, 2016.