Pericardial fluid profiles of pericardial effusion in systemic sclerosis patients

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Summary

Background: **Cardiac involvement is one of clinical presentations in systemic sclerosis (SSc). The pericardial fluid profile and the causes of pericardial effusion were our focus.**

Objectives: **To demonstrate the characteristics and causes of pericardial effusion in SSc.**

Methods: **A descriptive retrospective study was performed on SSc patients with symptomatic pericardial effusion at Srinagarind Hospital, Khon Kaen University, Thailand, between January 1, 2000 and December 31, 2010. We excluded pericardial fluid detected by screening echocardiography.**

Results: **Thirty medical records of SSc patients with pericardial effusion were reviewed. The respective mean age and median duration of disease at the time of effusion detection was 52.2±10.8 years and 11.4 months (IQR 0.03-59.1). The female to male ratio was 3.3:1. The most common signs and symptoms included tachycardia (65%) and right-sided heart failure (30%). One patient was diagnosed with cardiac tamponade due to tuberculous pericarditis. Pericardiocentesis and fluid analysis were performed in 9 patients, all of whom had pericardial fluid lactate dehydrogenase (LDH) >200 U/L and a fluid-serum LDH ratio >0.6. Most of the cases (87.5%) had a fluid-serum total protein ratio >0.5. The median white blood cell (WBC) count was 10 cell/mm^3 (IQR 6-830), one-third of which was predominated by mononuclear cells. The pericardial biopsy in 8 patients revealed 4 pericardial fibrosis, 2 non-specific inflammation and 2 granuloma.**

Conclusions: **The pericardial fluid profile for SSc was similar to the exudative profile of pleural fluid. Cardiac tamponade was rare. Most pathological findings of pericardial tissue were associated with fibrosis related to the disease itself.** ***(Asian Pac J Allergy Immunol 2013;31:314-9)***

Key words: *Systemic sclerosis, scleroderma, pericarditis, pericardial effusion, pericardium, autoimmune disease*

Introduction

Systemic sclerosis (SSc) is an uncommon connective tissue disease characterised by excessive collagen deposition on the skin and internal organs.[1] Cardiac involvement is one of the most serious internal organ involvements in SSc patients because of an associated high mortality rate.[1,2] Cardiac involvement is reported in at least 15% of SSc patients[1] but the prevalence is significantly higher after autopsy[3,4]: the manifestations could be systolic dysfunction, diastolic dysfunction, heart failure, pericardial effusion, cardiac fibrosis or conduction defect.[5,6]

Pericardial effusion and pericarditis were the presentations of pericardial involvement in SSc (prevalence, 7-20%)[7]; however, the true prevalence of pericardial involvement was probably underestimated owing to occult cardiac involvement.[8,9] Clinically symptomatic pericardial disease is much less frequently found than autopsy-demonstrated pericardial involvement (33-72%).[10] Clinical presentations of pericardial involvement in SSc vary from asymptomatic to right-sided heart failure. Despite years of observation and research, the cause of pericardial effusion and the characteristics of the pericardial fluid profile in SSc are not well understood. The objectives of this study were to demonstrate the characteristics and causes of pericardial effusion in SSc.

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Methods

A descriptive, retrospective study was performed in SSc patients, with symptomatic pericardial effusion. The study was conducted at Srinagarind Hospital, Khon Kaen University, Thailand, between January 1, 2000 and December 31, 2010. We excluded patients on whom echocardiography screening for pulmonary arterial hypertension was performed and those diagnosed with overlap syndrome.

We reviewed the clinical data for age, body mass index, disease duration, clinical presentation, history of contact with pulmonary tuberculosis, underlying diseases, echocardiographic parameters, findings from chest radiography, pericardial fluid profiles, pericardial tissue pathology, and medical treatment. The categorical data were reported as percentages and the continuous data as a mean±SD.

A diagnosis of systemic sclerosis (SSc) was based on the American College of Rheumatology Criteria.[11] SSc was classified as the limited or diffuse subset as per the classification by LeRoy et al.[12] Pericardial effusion was diagnosed by echocardiography and the amount of fluid in the pericardium measured by the distance between the epicardium and the pericardium. The amount of pericardial effusion according to the effusion thickness was classified as minimal (<0.5 cm), moderate (0.5–2 cm) or large (>2 cm). Tachycardia is defined as a heartbeat greater than 100 beats/minute. Cardiac tamponade was diagnosed if the patient had the following conditions: low blood pressure, pulsus paradoxus, early diastolic collapse of the right ventricle and right atrium (based on echocardiographic findings). Pulmonary arterial hypertension was considered fulfilled if the echocardiogram estimated right ventricular systolic pressure (RVSP) was greater than 40 mmHg. Impaired left ventricular function was fulfilled if the left ventricular ejection fraction (EF) was less than 60%.

The study was approved by the Khon Kaen University Ethics Committee with the reference number HE541311.

Results

A total of 702 medical records of SSc patients (420 females; 282 males) were reviewed. The majority (492 cases; 70%) were classified in the diffuse SSc subset; of whom 30 (4.3%) had symptomatic pericardial effusion and were included in our study. The mean age at onset of SSc in the patients with symptomatic pericardial effusion was 49.3±14.6 years (range, 17.5–78.9). The respective mean age and median duration of the disease at time of effusion detection was 52.2±10.8 years (range, 39.6–71.8) and 8.3 months (IQR 3.7-61.7). The female to male ratio was 3.3:1. Almost all of the cases belonged to the subset of diffuse SSc (29 cases; 96.7%) and the majority (82.4%) were anti-Scl70 positive.

The most common clinical presentations in which pericardial effusion was detected were tachycardia (65%), right-sided heart failure (30%) and fever (27%) (Table 1). Two of the 30 patients reported contact with tuberculosis in the year preceding the detection of pericardial effusion. None of the 30 had had any history of cardiac surgery. The majority of cases (83%) had moderate pericardial effusion. Only 1 patient developed cardiac tamponade and this patient was later diagnosed as having tuberculous pericarditis as per the classical pathology finding of caseous granulomatous inflammation. Impaired left ventricular function was detected in 16 cases (53.3%) with a mean EF 53.9±18.9% (range 15-86). The overall median RVSP was 32 mmHg (IQR 24-64). The pulmonary arterial hypertension was determined in 5 cases (16.7%), none of whom underwent right heart catheterisation to make a

Table 1. Clinical characteristics

Clinical characteristics	N = 30 (%)
Females	23 (76.7)
Clinical presentations	
Fever	8 (26.7)
Chest pain	2 (6.7)
Weight loss	4 of 6 (66.7)
Right-sided heart failure	9 (30)
Clinical signs	
Tachycardia	19 (63.3)
Pericardial friction rub	4 (13.3)
Cardiac tamponade	1 (3.3)
Electrocardiographic findings	
Electrical alternans	1 (3.3)
Low voltage	10 (33.3)
Widespread ST segment elevation	0
Amount of pericardial effusion	
Minimal	1 (3.3)
Moderate	25 (83.3)
Large	4 (13.3)

definitive diagnosis. Four of these patients had moderate pericardial effusion while the remainder had minimal pericardial effusion. Only 1 case of detected pulmonary arterial hypertension developed into right-sided heart failure coexisting with moderate pericardial effusion.

Pericardiocentesis was performed in 9 patients (30%). The pericardial fluid profile was similar to the exudative profile of pleural fluid. All had pericardial fluid lactate dehydrogenase (LDH) >200 U/L and a fluid-serum LDH ratio >0.6. Most of the cases (87.5%) had a fluid-serum total protein ratio of >0.5. The median white blood cell (WBC) count was 10 cell/mm^3 (IQR 6-830), one-third of which were mononuclear cells. The antinuclear antibody test was positive in 50% of cases and 1 had a positive polymerase chain reaction (PCR) for tuberculosis in the pericardial fluid. The difference in the clinical characteristics and pericardial fluid profiles between pericarditis due to infection and non-infection are presented in Table 2.

Table 2. Difference between clinical and fluid characteristics of pericarditis due to infective and non-infective pericarditis

Data	Non-infective pericarditis N = 28	Infective pericarditis N = 2
Clinical characteristic		
Fever	8 (28.6%)	1 (50.0%)
Chest pain	1 (3.6%)	0
Right sided heart failure	8 (28.6%)	1 (50.0%)
Amount of effusion		
Minimal	1 (3.6%)	0
Moderate	24 (85.7%)	1 (50.0%)
Large	3 (10.7%)	1 (50.0%)*
Pericardial fluid profiles	N = 7	N = 2
Total WBC count (median; IQR)	10 (0-830)	1,030 (10-2050)
WBC >1,000/mm^3	1 (14.3%)	1 (50.0%)
Sugar	111 (82-139)	103 (75-131)
Protein	5.3 (4.1-6.0)	147.6 (5.1-290)
Fluid:serum protein ratio > 0.6	4 (57.1%)	2 (100.0%)

WBC; white blood cell, IQR; interquartile range

*large volume of pericardial fluid with clinical signs indicating cardiac tamponade

A pericardial biopsy was performed in 8 patients, of whom 4 (50%) had pericardial fibrosis, 2 (25%) granuloma and 2 (25%) non-specific inflammation. Only 1 patient who underwent biopsy also underwent serological testing from the pericardial fluid: the result showed a high titre of antinuclear antibodies (ANA) in the pericardial fluid and the patient had pericardial fibrosis.

Most of the patients who had pericardial fibrosis and non-specific inflammation died within 1 month of having a pericardial biopsy. None of those with granuloma died. The treatments and outcomes of treatment, categorised by pathological findings, are presented in Figure 1 and Table 3.

The clinical differentiation between the patients who were anti-Scl70 positive and negative is presented in Table 4.

Discussion

Symptomatic pericardial effusion was rare in our SSc patients. We observed that <15% of the patients presented with typical signs and symptoms of pericarditis (*i.e.,* chest pain, pericardial friction rub, and widespread ST-segment elevation by electrocardiography), but that most had non-specific signs and symptoms (*i.e.,* constitutional symptoms and tachycardia). Since the typical signs and symptoms of pericarditis are the manifestations of acute pericarditis[13], it is possible that the natural course of pericardial disease in SSc has an insidious onset and slow progression. We suggest considering pericardial disease in patients with SSc with unexplained tachycardia and constitutional symptoms, even if they have no typical signs and symptoms of pericarditis.

In most of our patients, pericardial effusion was detected within the first year of the disease. According to the natural course of SSc, disease progression such as skin tightness and internal organ involvement are revealed within the first 3-5 years and are associated with mortality.[1,14,15] It is not surprising, therefore, that symptomatic pericardial effusion was detected in the first year of the disease.

The pericardial fluid profile has rarely been extensively evaluated in SSc patients. Most reports were case series or case reports.[18–22] This may be related to the relatively rare presentation of moderate to grave pericardial effusion in SSc or the risk of major complications related to the pericardiocentesis procedure in SSc patients, particularly those with poor skin elasticity of the chest wall or pulmonary arterial hypertension[23]; this

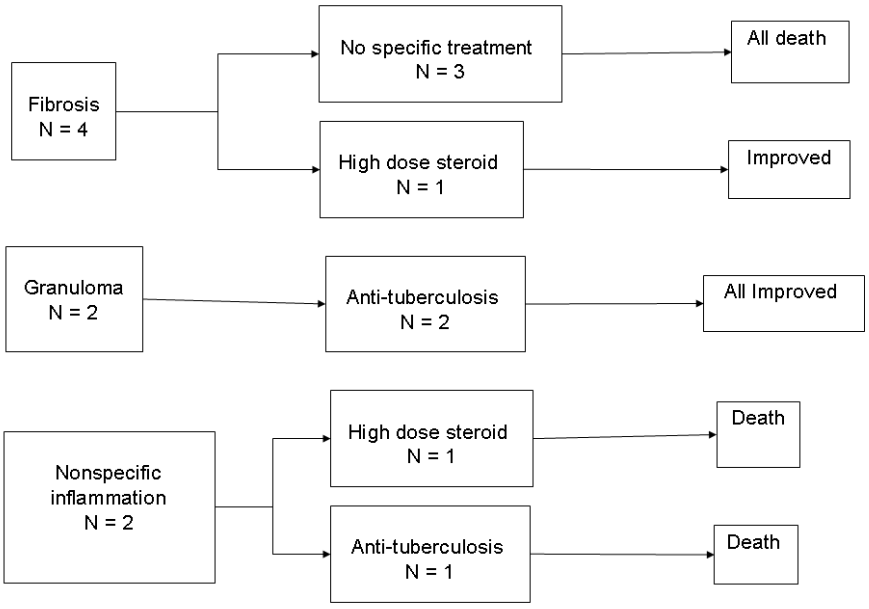

Figure 1. Treatment of pericardial effusion categorized by pericardial pathological findings

was the reason why more than half of our patients did not undergo the invasive procedure and instead had their pericardial fluid profile evaluated. Therefore, this is the first study to include a large number of analyses of pericardial fluid and pericardial pathological findings from patients with SSc.

It is possible that inflammation was a major mechanism of pericardial involvement in SSc, particularly during the early onset of the disease. Although we only evaluated 9 cases of pericardial effusion, the findings provide some insight on trends. The characteristic of pericardial fluid in all of our SSc patients was consistent with the exudative profile with low cell count, high protein and high lactate dehydrogenase, according to the classification for pleural effusion in Light's criteria,[24] despite having excluded pericarditis due to infection. The pericardial profile in our observation was not different from the previous reports.[18,25] However, there are no data on the inflammatory mechanism, such as the role of the complement, the humoral immune response, or the cellular immune response toward pericardial disease in patients with SSc. The inflammatory process of pericardial effusion in SSc should therefore be further investigated.

Table 3. Treatment and outcome of the patients who did the pericardial biopsy

Patient number	Pericardial pathological findings	Co-morbid disease	Treatment	Outcome	Cause of death
1	Pericardial fibrosis	None	None	Death	Cardiac arrhythmia
2	Pericardial fibrosis	Right sided heart failure	None	Death	Right-sided heart failure
3	Pericardial fibrosis	Diabetes mellitus, right sided heart failure	None	Death	Right-sided heart failure
4	Pericardial fibrosis	Pulmonary fibrosis	High dose steroid	Improved	-
5	Nonspecific inflammation	None	High dose steroid	Death	Renal crisis
6	Nonspecific inflammation	Right sided heart failure	Anti-tuberculosis	Death	Pneumonia
7	Granuloma	Cardiac tamponade	Anti-tuberculosis	Improved	-
8	Granuloma	None	Anti-tuberculosis	Improved	-

Table 4. Clinical differentiation between anti-Scl70-positive and -negative patients

Clinical characteristics	Anti-Scl70-positive N = 16	Anti-Scl70-negative N = 3
Duration of disease at time of pericardial effusion detection (months; median, IQR)	8.3 (4.9-21.6)	1.0 (0.2-7.0)
Amount of pericardial effusion		
Moderate	14 (87.5%)	3 (100%)
Large	2 (12.5%)	0
Pericardial fluid profiles	N = 5	N = 1
Total WBC count (median; IQR)	10 (6-10)	39
Sugar	111 (82-131)	137
Protein	5.6 (4.6-6.5)	2.7
Fluid:serum protein ratio >0.6	5 (100%)	0
Pathological findings	N = 5	N = 1
Nonspecific inflammation	1 (20%)	1 (100%)
Pericardial fibrosis	4 (80%)	0

A high white blood cell count in the pericardial fluid and a fluid-to-serum protein ratio >0.6 seems to be related to an infectious rather than a non-infectious process. The sugar level in the pericardial fluid does not explain the difference between the infectious and non-infectious process. Due to our small sample size and the descriptive nature of the study, we are not able to draw any conclusions; nevertheless, the findings could be helpful for the attending physician treating patients with infectious pericarditis in whom a high fluid-to-serum protein ratio and a high white blood cell count are observed.

The common pericardial pathology in our sample of SSc was consistent with pericardial fibrosis, which was a major pathological finding of the disease despite having an exudative pericardial fluid profile. Moreover, the finding was more common in patients who were anti-Scl70-positive, which was related to the early and extensive internal organ fibrosis. Non-specific inflammation may, however, be revealed.[7] According to our observations, the outcome of treating pericardial disease in SSc patients was not good, except among patients with pathological findings consistent with tuberculosis. Patients died after high-dose steroid therapy, despite bringing down the inflammation. Since we analysed the treatment outcomes from a small sample, we cannot conclude what role steroid therapy or any other inflammatory agents play in pericardium disease in SSc. Although there is no clear evidence of the treatment of choice for pericardium disease in SSc, our observations do provide some interesting information and help for guiding further investigations.

In our observation, moderate pericardial effusion was most commonly detected, whereas large pericardial effusion usually led to cardiac tamponade, which is a rare manifestation in both diffuse and limited SSc subsets.[19,26] The association between cardiac tamponade and pulmonary arterial hypertension or renal disease with a poor outcome in SSc has been documented.[18,19,27] In contrast, according to our observations, pulmonary arterial hypertension and renal disease are rarely associated with large pericardial effusion or cardiac tamponade. Only 1 of our patients presented with cardiac tamponade, which was shown to be the result of tuberculous pericarditis without any evidence of pulmonary arterial hypertension or renal disease. This finding could be explained by its occurrence in an endemic area for tuberculosis. Consequently, once cardiac tamponade is detected in an endemic area, an infectious process should be considered and pericardial drainage with pericardial tissue biopsy promptly performed in order to arrive at a definite diagnosis and rule out infective pericarditis because it is a curable disease.

Our study was limited by: (a) its retrospective nature; (b) the small sample with only a few occasions when pericardiocentesis or pericardial biopsy was performed; and, (c) the financial limitations which barred the use of some tests for all cases (*e.g.,* anti-centromere antibody, PCR for tuberculosis, pericardial immunofluorescence), meaning that we could not define some of the clinical associations that would have allowed a definite diagnosis. Our study nevertheless represents a pilot study that provides some interesting results. The findings may also describe the natural history of pericardial disease in patients with SSc and therefore serve as a guide for further research.

Conclusion

Symptomatic pericardial effusion in systemic sclerosis is a rare condition, mostly detected as effusion within the first year of diagnosis of systemic sclerosis, with non-specific signs and symptoms. The majority of our cases had moderate pericardial effusion, which is an exudative profile in which mononuclear cells predominated. The common pericardial pathology was consistent with

pericardial fibrosis, which was a major pathological finding in SSc.

Conflict of interest

The authors have no conflicts of interest.

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