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# Autopsy versus clinical findings in patients with systemic sclerosis in a case series from patients of the EUSTAR database

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## ABSTRACT

**Objective.** Subclinical organ pathology occurs regularly in systemic sclerosis (SSc) and affects correct prognosis as well as treatment choices.

We aimed to evaluate autopsy data for organ involvement with subsequent correlation to clinical data in order to assess discrepancies in pathological and clinical findings in SSc.

**Methods.** A standardised autopsy questionnaire from diseased patients registered in the European Scleroderma Trials and Research group (EUSTAR) cohort was analysed on cause of death and various manifestations in different organ systems. Clinical data obtained from the EUSTAR database of the corresponding patients including cause of death and disease manifestations of lung, heart, kidney, gastrointestinal, skin or musculoskeletal organ involvement were retrospectively analysed and compared to autopsy data.

**Results.** 11 patients (6 women, 5 male) aged between 23 and 84 were included. Cause of death defined by pathologist and clinician were identical in 9/11 cases. In 8 individuals, cause of death was related to heart and lung pathologies. Heart and lung involvement (both 10/11) were the most frequently detected organ involvement at autopsy. Here, myocardial fibrosis occurred in 66% and lung fibrosis in 50% of the patients. Clinically, diastolic function abnormalities (6/11), conduction block (4/11), reduced DCLO (6/11) and dyspnea (8/11) were the most prevalent cardiopulmonary findings. For heart and renal involvement we found higher prevalence in autopsy than by clinical diagnosis. Especially myocardial fibrosis and renal arteriosclerosis were only obtained by autopsy in several individuals.

**Conclusion.** Clinical diagnostic procedures are limited in detection of end-organ damage, especially for cardiac

involvement. All the more post mortem examinations are needed for quality verification of clinical diagnosis and might help as to better understand the disease processes as well as to improve patient care.

## Introduction

Systemic sclerosis (SSc) is a multi-organ disease characterised by vasculopathy, low grade inflammation and overproduction of collagen (1). Besides the skin, heart, lungs, kidney and gastrointestinal tract are most notably affected. Mortality and morbidity of the disease are high, showing standardised mortality ratios ranging from 1.5 to 7.2 (2, 3). In over 50% of cases, deaths in SSc patients are related to SSc directly, followed by death due to malignancy, infections, gastrointestinal haemorrhages, cardiovascular causes and treatment related mortality (2, 4, 5). Cardiac and pulmonary affection with 19% due to pulmonary fibrosis, 14% to pulmonary arterial hypertension (PH) and 14% to myocardial disease are considered as the main killers in SSc (3, 4). Cardiac, pulmonary and renal involvement as well as age at onset of Raynaud's phenomenon, the modified Rodnan skin score, Scl-70, older age at onset and male gender were found to increase the risk of mortality (2-4).

Today's diagnostic modalities such as high resolution computed tomography (CT), echocardiography or right heart catheter facilitate the detection of clinically unapparent organ involvement in SSc (6, 7). However, it is well known that subclinical organ affection such as fibrosis of the heart regularly occurs (8). This is not only important for the correct prognosis for the patient, but also affects the treatment choices, e.g. the maximal cyclophosphamide dose in or outside autologous haematopoietic stem cell transplantation settings (9).

Autopsy is an essential tool for quality verification of clinical diagnosis as well as treatment evaluation (10, 11). Unfortunately, autopsies are performed less frequently (10).

In general, discrepancies between clinical and autopsy results focusing on main diagnosis and on cause of death were described in the past (10, 12, 13) with discrepancy rates for cause of death up to 63% (13) and for main diagnosis up to 33.6% (12).

In this study, we investigated autopsy results obtained by a comprehensive questionnaire in SSc patients registered in the European Scleroderma Trials and Research (EUSTAR) database and compared them to their clinical data both describing cause of death and non-fatal SSc-related comorbidities.

### Patients and methods

In July 2014, the EUSTAR database was reviewed for deceased SSc patients. The structure and content of the dataset is described elsewhere (14). All

participating centres were invited to fill out a standardised autopsy questionnaire (supplementary data) for patients who underwent autopsy. The questionnaire assessed various organ systems as well as cause of death declared by pathologist and clinician and whether the death was related to SSc.

Clinical information was obtained from the database and included disease manifestations of lung, heart, kidney, gastrointestinal, skin or musculoskeletal organ involvement.

Returned autopsy surveys we compared with the corresponding clinical data from the EUSTAR database. Dyspnea was defined as New York Heart Association (NYHA) Grade 3 or 4, arterial hypertension as blood pressure >140mmHg systolic or >90mmHg diastolic. Pulmonary fibrosis was diagnosed by CT. Lung restriction was defined as vital capacity <80%. PH (defined as systolic pulmonary artery pressure >40 mmHg), diastolic dysfunction and reduced left ventricular ejection fraction

(LVEF) were diagnosed according to echocardiographic results.

### Results

#### Patients

We received autopsy reports from eleven patients, who deceased between 2007 and 2014. Six patients were female and five male. Eight suffered from diffuse (dcSSc) and three from limited SSc (lcSSc). Three patients underwent prior haematopoietic stem cell transplant (HSCT), one had received lung transplant. All except one patient fulfilled the former ACR criteria. Other demographic features can be seen in Table I.

#### Cause of death

Cause of death defined by pathologist and clinician were identical in nine out of eleven cases (Table I). In one case, the final cause of death remained undetermined by pathologist because of missing histological data, in one case cause of death was not reported in the survey. Seven deaths were defined as SSc-relat-

**Table I.** Demographic and serological characteristics, treatment and cause of death of the 11 patients included from the EUSTAR database.

Patient	1	2	3	4	5	6	7	8	9	10	11
Age at death (years)	67	57	68	27	45	23	65	50	70	57	84
Sex	Female	Male	Female	Female	Male	Male	Male	Female	Female	Female	Male
Clinical subtype	Diffuse	Diffuse	Diffuse	Diffuse	Diffuse	Diffuse	Diffuse	Diffuse	Limited	Limited	Limited
Autoantibodies +	ANA, Anti-Scl-70	ANA, Anti-Scl-70	ANA, Anti-Scl-70	nd	ANA	ANA, Anti-Scl-70	ANA	ANA, Anti-Scl-70	ANA, ACA	ANA, ACA	ANA, ACA
Age at onset of RP	65	53	57	24	45	22	31	19	64	35	72
Age at onset of non-RP	67	53	57	24	44	22	30	25	64	28	82
Medication	Pred, NSAID, DIU, CCI, ACE-I	ND	ND	MYC, INN	PPI, CCI, antiplatelet-aggregant	PPI, CCI	ND	ND	ND	Pred, AZA, ERA, PDE-5-I, PGI <sub>2</sub> , PPI, DIU	ND
Other treatment	HSCT				HSCT	HSCT				Lung Tx	
Cause of death by pathologist	Cardio-pulmonary insufficiency	Diffuse alveolar damage	Pulmonary fibrosis	Cardiac tamponade	Pneumonia, pulmonary oedema, pericarditis myocardial ischaemia	Myocardial ischaemia	Cerebral bleeding	ND	ALS ventilatory failure	Diffuse alveolar damage	Not determined histologically
by clinician	Cardio-pulmonary insufficiency	Pulmonary infection	Pulmonary fibrosis	Cardiac tamponade*	Multiorgan insufficiency	Myocardial insufficiency	Cerebral bleeding	ND	ALS with ventilatory failure	Aspiration pneumonia and sepsis	Pulmonary oedema/ cardiac failure
Death due to SSc by pathologist	+	+	+	-	+	+	-	ND	-	-	ND
by clinician	+	+	+	-	+	+	-	+	-	+	-

ACA: anticentromere antibodies; ACE-I: angiotensin-converting-enzyme inhibitor; ALS: amyotrophic lateral sclerosis; ANA: antinuclear antibodies; ARC: American College of Rheumatology; AZA: azathioprine; CCI: calcium channel blockers; DIU: diuretics; ERA: endothelin receptor antagonist; HSCT: hematopoietic stem cell transplantation; INN: imatinib; MYC: mycophenolate; ND: no data available; NSAID: nonsteroidal anti-inflammatory drug; PDE-5-I: phosphodiesterase type 5 inhibitor; PGI<sub>2</sub>: prostacyclin; PPI: proton pump inhibitors; Pred: prednisone; RP: raynaud's phenomenon; SSc: systemic sclerosis; Tx: transplant; + ever reported; \* after pericardial puncture.

ed by the clinician, whereas only five deaths were classified as SSc-related by the pathologist after autopsy. In two cases, no statement of pathologists was given and in one case there was a dissent. In the patient, who underwent prior lung transplantation, the clinician referred aspiration pneumonia due to SSc with subsequent sepsis, whereas respiratory distress syndrome/diffuse alveolar damage related to the lung transplant was diagnosed by the pathologist. SSc-related causes of death reported by the pathologist were cardiopulmonary insufficiency, myocardial ischaemia, subacute diffuse alveolar damage, bilateral bronchopneumonia in combination with myocardial ischaemia and usual interstitial pneumonia. The four non-SSc-related deaths were postinterventional cardiac tamponade, cerebral bleeding, amyotrophic lateral sclerosis with ventilatory failure and respiratory insufficiency secondary to cardiac failure. Three of the patients, who died from SSc-related complications, deceased after haematopoietic stem cell transplantation (HSCT).

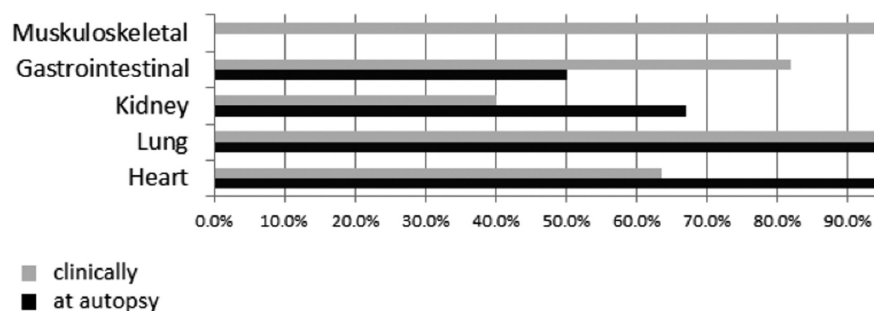
#### Organ manifestations

Data for organ weights were available in seven autopsy reports: Heart weight ranged from 270g to 630g (normal male 280–340g, female 230–280g), thus in all except one patient the heart weight was increased. Lung weight reported in four patients ranged from 450g to 800g (normal 500g). The kidneys' weight ranged from 100g to 206g (normal 120–200g) and was only marginally elevated in one patient. The liver weight ranged from 1150g to 2222g (normal 1400–1600g), and the spleen weight from 138g to 430g (normal 150–200g), indicating regular hypertrophy of both organs.

Musculoskeletal and gastrointestinal organ affection by SSc were more frequently diagnosed clinically, whereas heart and kidney damage was more often detected in autopsy (Fig. 1). Lung damage was equally well diagnosed by the clinician and pathologist.

**Heart.** In ten out of eleven autopsy reports  $\geq 1$  pathological cardiac finding was reported. Myocardial fibrosis and coronary arteriosclerosis (both in 5 out of 11 patients) were most frequently

#### Organ manifestations



**Fig. 1.** Relative occurrence of different organ involvement related to those patients for whom data on at least one symptom of the particular organ system were available.

detected. 3/5 patients with myocardial fibrosis also suffered from coronary arteriosclerosis and 4/5 from generalised atherosclerosis at autopsy. Clinically only 3/6 patients with myocardial fibrosis had conduction block or diastolic failure and only one of the patients suffered from palpitations. Autopsy revealed cor pulmonale in two patients. Both of them also had interstitial lung fibrosis and PH was previously diagnosed by the clinician.

None of the three cases of pericardial effusion at autopsy was diagnosed clinically. All three of them also had pleural effusion, potentially indicating a right heart dysfunction as underlying cause of pericardial effusion. The cause of death of those three was cardiopulmonary insufficiency in two cases and diffuse alveolar damage in one case.

Data for left and right ventricle wall thicknesses were reported for four patients and ranged from 4 to 18mm (normal 8–12mm) and from 1 to 5mm (normal 3–5mm), respectively. The patient with 18 mm left ventricular-wall thickness clinically suffered from diastolic dysfunction, conduction block and coronary arteriosclerosis.

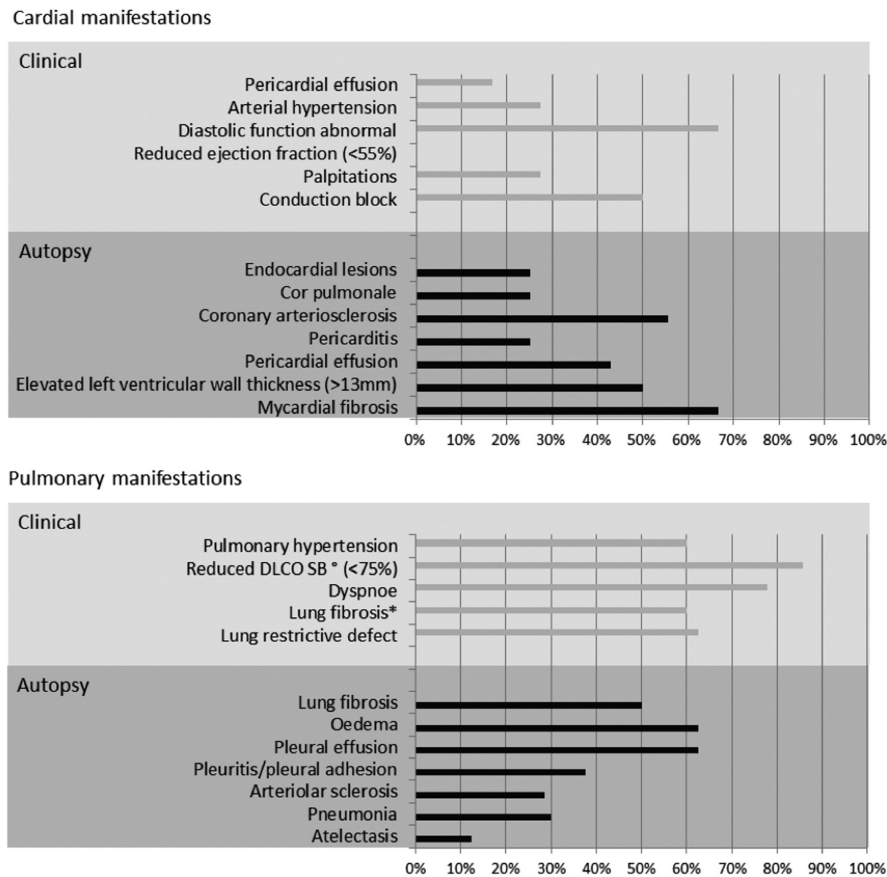
**Lung.** In 10/11 autopsy reports,  $\geq 1$  pathological pulmonary finding was described. Five autopsy reports indicated interstitial lung fibrosis. All of them were also diagnosed clinically. In one case, lung fibrosis diagnosed by CT was not confirmed at autopsy. Except one, all patients with lung fibrosis suffered from dyspnea, whereas reduced DLCO and lung restrictive defect were reported in only three cases. Conversely, three patients with reduced DLCO did not have lung fibrosis but PH, lung oedema

or pleural effusion at autopsy. Restrictive pulmonary defects in the absence of fibrosis were diagnosed clinically in two further patients; one had pleural adhesions and the other amyotrophic lateral sclerosis.

Pulmonary oedema at autopsy was detected in five patients. All of those had myocardial, pericardial or endocardial SSc involvement. He deceased because of cerebral bleeding. Pleural effusion was described in five autopsies, in three cases, pericardial effusion was detected. Bronchiectasis, emphysema, lung infarction or bronchial congestion was not reported at autopsy.

**Gastrointestinal tract (GIT).** Oesophageal abnormalities were described in three autopsy reports. Two patients had oesophageal fibrosis either alone or in combination with oesophageal ulceration. In the remaining eight autopsy reports, no oesophageal abnormalities such as muscle atrophy or Barrett's metaplasia were described. All three patients with oesophageal pathologies suffered from symptoms. 4 other patients, who had oesophageal symptoms did not show any oesophageal findings at autopsy. Only one autopsy report indicated muscle atrophy of the small and large intestine in an asymptomatic patient affected by amyotrophic lateral sclerosis (ALS). On the other hand, five patients, who suffered from intestinal symptoms had no abnormal finding at autopsy.

**Kidney.** Autopsy revealed pathological findings in 4 cases. In two patients with reduced kidney size and intimal thickening respectively, proteinuria was described clinically. In the other two patients with renal arteriosclerosis and



**Fig. 2.** Relative occurrence of a specific clinical or autopsy finding for cardiac and pulmonary manifestations related to those patients for whom the particular manifestation was examined.

\* diagnosed by x-ray and/or HRCT; °  $D_{LCO}^{SB}$ , single-breath diffusing capacity of the lung for carbon monoxide.

kidney hypertrophy, no pathological clinical data was reported. Interestingly, the only patient who presented with acute renal failure had no pathological renal finding at autopsy. Glomerulonephritis, interstitial nephritis or other kidney changes were not reported.

**Malignancies.** Two autopsy reports described malignancies. In one case, an incidental papillary carcinoma of the gallbladder and benign leiomyoma of uterus were found. In the other patient, a clinically silent adenocarcinoma in the mesentery of unknown primary site was detected.

**Other findings.** In one autopsy, pathological bone marrow changes were described. This patient died one day after HSCT. Cerebral lesions were found in three autopsies showing oedema, anoxic-ischaemic encephalopathy and amyotrophic lateral sclerosis lesions, respectively. Three patients had thyroid fibrosis. In contrast, arteritis, pancreatic fibrosis, skeletal muscle atrophy, ad-

renal atrophy, spleen or brain involvement were not observed.

### Discussion

In this study, we compared the results of autopsy findings in patients with SSc with clinical data obtained before death in the setting of the EUSTAR database. In several individuals, end organ damage of SSc, notably myocardial fibrosis was only found at autopsy, but not clinically. This is important as it shows that despite modern diagnostic tools, occult organ affection in SSc is still frequent. This is in line with other studies *e.g.* showing myocardial SSc involvement in 80–90% of patients (15), often despite normal ECG and normal left ventricular systolic function. SSc-associated vasculopathy with concentric intimal hypertrophy and myocardial fibrosis can be seen in heart biopsies of SSc patients despite normal left ventricular function. Thus, more sophisticated cardiac imaging procedures such

as Doppler or MRI as well as biopsies of lung and heart might be warranted in patients with SSc (16). On the other side, diagnostic sensitivity of endomyocardial biopsy has been reported to be of limited value due to sampling error and invasiveness (17). Non-invasive diagnostic procedures for the detection of heart fibrosis are attractive. Unfortunately, neither cardiac symptoms nor ECG or heart echography consequently predicted heart fibrosis in the here reported patients. Other reports indicate similar findings with left ventricular systolic dysfunction being a rare finding in SSc patients, with only 5% of patients affected by reduced EF (18). Conversely, diastolic dysfunction as detected here in 5/11 patients was higher than reported in the EUSTAR database (17.4%) (19) and likely due to patient selection. According to other studies, 24-hour monitoring or exercise ECG, both not obtainable in this study, seem more appropriate to detect conduction system abnormalities and arrhythmias compared to conventional ECG (20).

Interstitial lung fibrosis in this study was encountered in 45% of the patients, which is similar to previous reports (21, 22). Also similar to other studies, in the case series here, dyspnea predicted lung fibrosis in 100% but was unspecific as symptom as it might be related to pulmonary vascular disease, cardiac involvement or musculoskeletal involvement of the patients (23).

The cause of death in this case series was mostly related to SSc-associated heart and lung pathologies, which is also in line with previous studies (4, 5). In a few cases, there was a dissent between clinician and pathologist whether pneumonia or structural lung damage due to SSc caused death. Undiagnosed pneumonia in a multi-morbid patient, as it occurred in two patients in this study, might have fatal consequences. As a complex multi-system disease, discrepancies up to 63% between the treating physician and pathologist for the cause of death are not uncommon in SSc patients (13). One reason for this might be the fact that vascular events occurring in SSc patients are typically multifactorial, notably in the presence of cardiovascular risk factors. Potentially, it might be use-

ful to clinically differ between probable, possible and definite SSc related deaths as outlined by Hesselstrand *et al.* (5).

A particularity of this study was the fact that three patients underwent autologous HSCT. All of them died shortly after the procedure, yet the cause of death in form of cardiovascular insufficiency was attributed to SSc. Two of the three had myocardial fibrosis at autopsy, the third one had pericarditis. This might indicate that occult heart involvement in SSc patients might be a risk factor for HSCT. It was suggested to perform biopsies before autologous HSCT as to reveal potential clinically undiagnosed advanced cardiopulmonary involvement (24). As reported in the ASTIS trial, mortality after HSCT was substantially associated with smoking (25); the smoking status of the patients in this survey was not known.

The high prevalence of gastrointestinal symptoms in SSc patients reported in literature (26) is confirmed in this study for oesophageal symptoms (73%) and intestinal symptoms (55%) albeit oesophageal (27%) and intestinal involvement (9%) at autopsy was lower than reported elsewhere (oesophagus 74%, duodenum 48% and colon 39%) (22). Clinically undiscovered cancer was encountered during autopsy in two cases. One was adenocarcinoma of the gallbladder and the other adenocarcinoma of unknown primary site in the mesentery. Both were not considered as cause of death. The influence of these tumours on the SSc manifestations cannot be clarified in this study. Clearly, this study is too small to comment on prevalence of occult malignancies in SSc. Previous studies have shown increased risk of cancer in SSc patients with non-small cell lung cancer as the most prevalent malignancy (27). The mortality rate related to neoplastic pathologies among non-SSc related deaths is reported to range between 13% and 27.5% (2, 4). Limitations of this study are the heterogeneity of patients, data inconsistency and notably treatment regimens. One patient priorly underwent lung transplant and thus received additional immunosuppression, three patients had HSCT. Thus, our cohort might differ from the general SSc population in the

spectrum of complications and organ manifestations of SSc.

Notwithstanding, this small case series demonstrates the limitations of clinical diagnostic procedures to detect end-organ damage. Autopsies might help to educate the clinicians, who treat severe SSc to better understand the disease and improve patient care.

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