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A Case Study and National Database Report of Progressive Systemic Sclerosis and Associated Conditions

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Case Study

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ABSTRACT

We report the case of a 34-year-old white woman with a history of progressive systemic sclerosis (PSS) and diffuse alveolar hemorrhage (DAH) that may be either a rare complication of PSS or induced by D-penicillamine. The DAH progressed to hemoptysis and led to intubation for airway protection. The patient progressed to acute renal failure. Her chest x-ray revealed diffuse bilateral infiltrates. She developed pulmonary fibrosis with secondary pulmonary hypertension. She experienced a brief period of improvement of her respiratory status after steroid treatment. We also report a database of 21,442 decedents with PSS over a 15-year period from 1979 to 1994. Our report demonstrates that of over 21,000 decedents, only 0.2% had pulmonary hemorrhage or hemoptysis or both listed as a cause of death. The data also demonstrate that PSS was the underlying cause of death more frequently in younger people. Age-adjusted mortality rates were higher for blacks than for whites and for women than for men.

INTRODUCTION

PROGRESSIVE SYSTEMIC SCLERODERMA (PSS) is a connective tissue disease that rarely is associated with diffuse alveolar hemorrhage (DAH). We report a case of PSS with DAH that may be penicillamine induced. We include an analysis of a large database from the Centers for Disease Control and Prevention's National Center for Health Statistics (NCHS), demonstrating mortality trends in decedents with PSS and associated pulmonary conditions.

CASE REPORT

The patient was a 34-year-old white woman with a history of PSS, admitted to the University of Kentucky Medical Center for hemoptysis and hypoxemia. She had been initially diagnosed with the disease 6 months before admission and had been receiving penicillamine, 250 mg orally twice a day, with varying results. Two weeks before this hospitalization, she had been started on oral methotrexate 740 mg/day. Several days before hospitalization, she had seen her local physi-

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cian with complaints of "congestion," tightness over her left anterior chest wall, and a slight cough. These complaints were followed by hemoptysis, nausea, and vomiting. She was found to be hypoxemic by an arterial blood gas sample ($\text{PO}_2 = 44$ mm Hg) obtained on 4 L/min via nasal cannula. She was subsequently intubated and transferred to the medical intensive care unit. She was initially given Solu-Medrol (Upjohn, Kalamazoo, MI) 30 mg intravenously four times daily. On admission to the intensive care unit, her blood pressure was 169/95 mm Hg, pulse rate was 140 beats/min, respiratory rate 40 breaths/min, and she was afebrile. Physical examination revealed bilateral crackles, tachycardia, and cyanosis of her upper and lower extremity digits. Digital ischemia, sclerodactyly, and telangiectasia of her upper extremity digits were noted. The skin of her face and digits was noted to be tight, thickened, and to possess a "shiny character." While intubated, she required 100% oxygen. Pulmonary artery catheter parameters revealed the following: central venous pressure 12 mm Hg, pulmonary artery pressure 40/24 mm Hg, cardiac output 6.0 L/min, cardiac index 3.5 L/min/m², pulmonary artery wedge pressure 12 mm Hg, systemic vascular resistance 1133 dyne/sec/cm⁵, and pulmonary vascular resistance 147 dyne/sec/cm⁵. Her chest radiograph demonstrated a diffuse, patchy interstitial process.

The patient underwent bronchoscopy with bronchoalveolar lavage (BAL), which demonstrated a bloody return from several segments. Although blood was noted throughout the airways on gross inspection, no endobronchial lesions were identified. No organisms were noted on stains or on culture. In addition, the patient's serum creatinine and urea levels were elevated (4.5 mg/dl and 90 mg/dl, respectively). Ultimately, she required hemodialysis. She also received plasmapheresis for a suspected pulmonary-renal syndrome. A serum electrophoresis was obtained, and results were consistent with an acute inflammatory response. Echocardiogram demonstrated normal left and right ventricular chamber size and motion. The patient developed parameters consistent with disseminated intravascular coagulopathy (DIC), as noted by an increase in her protime to 18.9 seconds, prothrombin time >100 seconds, and elevated fibrin degradative products (>10<40 $\mu\text{g/ml}$). Platelet counts were repeatedly in the low 50,000 range. A renal biopsy could not be obtained because of bleeding diathesis. Antinuclear cytoplasmic anti-

bodies and antiglomerular basement membrane antibodies were not present. The patient was given high-dose steroid therapy (Solu-Medrol 1 g intravenously daily), with a brief resolution of hemoptysis. Two days later, she began having massive hemoptysis and hypoxemia that was unresponsive to 100% oxygen and transfusions of red blood cells and fresh frozen plasma. She died shortly thereafter.

MATERIALS AND METHODS

The NCHS annually compiles data from all death certificates filed in the United States, using the vital records from the individual states. These data contain the International Classification of Diseases (ICD) codes for the underlying cause of death and up to 20 conditions listed on the death certificate. The data also include demographic and geographic information on the decedent. The International Classification of Disease, Ninth Revision (ICD-9) was implemented in 1979 and was in effect throughout the 15-year period of this study. The conditions are recorded in two places: on the entry axis, which contains the conditions exactly as reported on the death certificate, and on the record axis, which is edited by a computerized algorithm known as the translation of axes (TRANSAX). The automated classification of medical entities (ACME) algorithm determines the underlying cause of death (UCD) from the conditions and their positions as listed on the death certificates. Quality assurance of the data is maintained by trained nosologists who code conditions at the state level and, in turn, by nosologists at NCHS who periodically review data from a 10% sample of the submitted death certificates. The result of this process is the Multiple Cause Mortality File (MCMF).¹

We searched the record axis portion of the 1979–1994 MCMF for records containing ICD code 710.1: Progressive Systemic Sclerosis as either the UCD or as a comorbid condition. Within this group of death records, we searched for the UCD and comorbid conditions including lung cancer (ICD-9 162–162.9), chronic obstructive pulmonary disease (ICD-9 492–496), pulmonary fibrosis (ICD-9 515 or 516.3), sepsis (ICD-9 38–38.9), renal failure (ICD-9 584–586.9), respiratory failure (ICD 9 518.8), pneumonia (ICD-9 480–487.9), pulmonary hypertension (ICD-9 416–416.9), atherosclerotic cardiovascular disease (ASCVD, ICD-9 435–442.9 or 410–414.9), congestive heart

TABLE 1. AGE STRATIFICATION FOR DEATH IN THE UNITED STATES FOR PEOPLE WITH SCLERODERMA AND FROM ALL CAUSES COMBINED, 1979–1994^a

Age (years)	Total decedents	No. of decedents with scleroderma	Proportion per 100,000 decedents	Scleroderma as underlying cause of death	
				No.	%
<1	629,211	12	1.9	2	16.7
1–14	267,085	26	9.7	21	80.8
15–14	635,738	168	26.4	137	81.5
25–34	884,738	615	69.5	478	77.7
35–44	1,184,656	1,483	125.2	1,105	74.5
45–54	1,980,322	2,722	137.5	1,918	70.5
55–64	4,330,482	5,256	121.4	3,351	63.8
65–74	7,639,067	6,469	84.7	3,919	60.6
75–84	9,174,909	3,899	42.5	2,126	54.5
>84	6,905,112	79	11.5	381	48.1
Total	33,631,320	21,442	63.8	13,438	62.7

^aData from the Multiple-Cause Mortality Files, National Center for Health Statistics.¹

failure (ICD-9 428–428.9), and pulmonary hemorrhage (ICD-9 786.3 or 516.1). We also searched the entire 1979–1994 database for the noted conditions for use in determining standardized mortality ratios.

The PSS group was analyzed according to age, gender, and race. The 1980 and 1990 U.S. census data and the 1994 intercensal estimate were used as denominators to calculate the rate for 1980, 1990, and 1994. Linear interpolation was used to find the denominator to calculate the rates for other years. We age-adjusted the data to the 1980 U.S. population.

We determined standardized mortality ratios (SMRs) by dividing the proportion of PSS decedents with the comorbid condition of interest by the estimated proportion of decedents in the general population (age, gender, and race adjusted to the PSS distribution) with that same condition. Thus, a condition present in 10% of PSS decedents but only 1% of total decedents would have an SMR of 10.

RESULTS

PSS was listed on the death certificates of 21,442 (0.06%) of 33,631,320 decedents during the study period, including 17,877 (83.4%) whites, 3,233 (15.1%) blacks, and 332 (1.6%) people of other races. Women accounted for 16,492 (76.9%) of these decedents. This diagnosis most frequently appeared among decedents aged 35–64 years (Table 1). PSS was listed as the underlying

cause of death in 13,438 (62.7%) of the 21,442 decedents with PSS. This was more likely to occur if the decedent was age 44 years or younger (Table 1).

Over the study period of 1979–1994, age-adjusted mortality rates varied by race and by gender (Fig. 1). The overall female/male age-adjusted mortality rate ratio was 3:1 for whites and 2:1 for blacks. Both black and white women demonstrated a slight upward trend in mortality rates over the study period. Age-specific mortality rates among whites showed a trend toward higher mortality rates among older ages in both men (Fig. 2) and women (Fig. 3). These rates increased through the study period among white

FIG. 1. Age-adjusted mortality rates for ICD-9 code 710.1 by race and sex. Rates are per 1,000,000 population.

FIG. 2. Mortality rates for white males for ICD-9 code 710.1 per 1,000,000 population.

FIG. 3. Mortality rates for white females for ICD-9 code 710.1 per 1,000,000 population.

women aged 65–84 years. Age-specific rates among blacks were highly variable because of the small number of deaths (data not shown).

When we compared the comorbidity of decedents with PSS with that of all decedents in the United States during 1979–1994, we found that decedents with PSS were more likely to have a diagnosis of pulmonary fibrosis, pulmonary hypertension, respiratory failure, renal failure, sepsis, and congestive heart failure and less likely to have a diagnosis of lung cancer, chronic obstructive, pulmonary disease (COPD), and ASCVD (Table 2). Pulmonary hemorrhage was a rare find-

ing (13 cases, or 0.2% of decedents). This diagnosis was listed more frequently among decedents with PSS than all decedents, although the confidence intervals included 1, and chance cannot be excluded as an explanation.

DISCUSSION

PSS is a connective tissue disease characterized by Raynaud's phenomenon (skin color changes of digits occurring in response to environmental cold exposure, associated with numbness and

TABLE 2. NUMBER OF DEATH CERTIFICATES AMONG 21,442 DECEDENTS WHO DIED WITH A DIAGNOSIS OF SCLERODERMA, 1979–1994^a

	Number	% of total	Standardized mortality ratio	95% Confidence intervals
Lung cancer	620	2.9	0.37	(0.34, 0.39)
COPD	978	4.6	0.58	(0.54, 0.61)
Pulmonary fibrosis	1,703	7.9	10.09	(10.01, 10.17)
Sepsis	1,283	6.0	1.37	(1.29, 1.44)
Renal failure	2,860	13.3	2.73	(2.63, 2.83)
Respiratory failure	625	2.9	5.26	(4.84, 5.67)
Pneumonia	2,157	10.1	1.50	(1.43, 1.56)
Pulmonary hypertension	1,841	8.6	12.46	(11.89, 13.03)
ASCVD	4,224	19.7	0.59	(0.58, 0.61)
Congestive heart failure	3,472	16.2	1.69	(1.64, 1.75)
Pulmonary hemorrhage	48	0.2	1.09	(0.78, 1.39)

^aScleroderma (ICD-9 710.1), lung cancer (ICD-9 162–162.9), pulmonary fibrosis (ICD-9 515 or 516.3), sepsis (ICD-9 38–38.9), renal failure (ICD-9 581–585.9), respiratory failure (ICD-9 518.8), pneumonia (ICD-9 480–487.9), pulmonary hypertension (ICD-9 416–416.9), atherosclerotic cardiovascular disease (ASCVD, ICD-9 435–442.9), congestive heart failure (ICD-9 428–428.9), and pulmonary hemorrhage (ICD-9 786.3 or 516.1). The ratios are 95% confidence intervals comparing these rates with those in all decedents in the United States in 1987. The data were obtained from death certificates of 29,042,213 decedents in the United States, 1979–1994, Multiple-Cause Mortality Files.

pain), digit ischemia, fibrotic atherosclerotic changes of internal organs, skin thickening of the hands, arms, and face, and pulmonary, renal, myocardial, and gastrointestinal involvement (esophageal dysmotility and small bowel involvement).²

Systemic sclerosis may be separated into two distinct groups based on the progression of skin thickening. Patients with aggressive, diffuse skin thickening that affects the distal extremities and face and that has a progression proximally are labeled as having diffuse PSS. These patients usually develop early visceral findings of the disease. Patients who develop skin thickening of the distal extremities and face may have a prolonged course (years) before the development of visceral disease. These patients are thought to have limited PSS.² Because of the rapid progression of skin thickening and the internal organ involvement, it is likely that our patient had the diffuse variant of PSS.

Rocco and Hurd³ reported data to show the incidence of PSS to be approximately 4.5–12 new cases per million population per year. The female/male ratio is 3:1, with most diagnoses occurring between ages 20 and 60.³ The incidence has been reported to peak in the fifth to sixth decades of life. Females acquire PSS more frequently than males. The ratio appears to vary, especially in childbearing years, by 15:1.⁴

The data presented in this report show that the mortality is highest in black women with PSS and lowest in white men (Fig. 1), which is consistent with the epidemiology of PSS prevalence.² The female/male ratio of PSS deaths during the 15-year period of 3:1 for whites and 2:1 for blacks is likewise consistent with known data on PSS prevalence. Among both men and women, mortality rates increased with increasing age (Figs. 2 and 3).

Pulmonary fibrosis and pulmonary hypertension are significant complications of PSS. Patients with limited cutaneous PSS may demonstrate pulmonary hypertension without the presence of pulmonary fibrosis. In contrast, pulmonary fibrosis may occur in both limited and diffuse cutaneous PSS.⁵ Although both of these serious respiratory diseases were listed on a minority of the PSS death certificates, they were listed at much higher rates than on all death certificates over the study period. Pulmonary hemorrhage was a rare pulmonary complication.

Decedents with PSS were more likely to have respiratory failure, sepsis, pneumonia, congestive

heart failure, and renal failure listed on the death certificate. This finding is consistent with the known comorbidity of PSS, related either to the disease itself or to its treatment. Conversely, COPD and lung cancer were listed less frequently among PSS decedents, suggesting either a protective effect of PSS for these diseases or other factors (i.e., patients with PSS may be less likely to smoke cigarettes).

In our report, the question arises whether hemoptysis and DAH occurred as a result of PSS or secondary to the exposure of D-penicillamine. D-Penicillamine has been noted to cause an acute pulmonary-renal syndrome (or Goodpasture-like syndrome) of diffuse alveolar hemorrhage to pulmonary hemoptysis in various diseases.⁶ In contrast, cases of PSS have been reported wherein DAH was present with and without renal involvement and with and without the presence of D-penicillamine.^{7–12} Unfortunately, baseline serum creatinine and urea levels were not obtained before D-penicillamine therapy was initiated in our patient, and an autopsy was not granted by her family. It is likely that the patient represents either of the two scenarios.

Because we obtained data from death certificates, it is impossible to distinguish between diffuse and limited PSS or even to establish that PSS was present. Masi et al.¹³ defined preliminary criteria for PSS in 1981. Epidemiologic studies obtained before 1980 were not specific for these criteria, and errors in definition of PSS and trends of occurrence may exist. In addition, this study is biased by the ability of the physician signing the death certificate to correctly place the appropriate underlying cause of death and contributing factors. Despite these shortcomings, though, these data are consistent with both the known complications of PSS and the known patterns of PSS prevalence in the U.S. population. Our findings reemphasize the point that PSS is a disease that primarily affects women.

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