Association of occupational exposure with features of systemic sclerosis

Isabelle Marie, MD, PhD,[a] Jean-François Menard, MD,[b] Anne-Bénédicte Duval-Modeste, MD,[c] Pascal Joly, MD, PhD,[c] Stéphane Dominique, MD,[d] Pierre Bravard, MD,[g] David Noël, MD,[h] Jean-François Gehanno, MD, PhD,[e] Michael Bubenheim, ScD,[f] Jacques Benichou, MD, PhD,[f] and Hervé Levesque, MD, PhD[a]

Rouen, Le Havre, and Elbeuf, France

Background: Occupational exposure is reported as playing a substantial causative role in systemic sclerosis (SSc).

Objective: We sought to compare the characteristics of SSc in patients with and without occupational exposure to crystalline silica/solvents.

Methods: In all, 142 patients with SSc were enrolled in this prospective study. An expert committee performed blind evaluation of occupational exposure to crystalline silica/solvents.

Results: Patients exposed to crystalline silica more often exhibited: diffuse cutaneous SSc (P = .02), digital ulcers (P = .05), interstitial lung disease (P = .0004), myocardial dysfunction (P = .006), and cancer (P = .06). Patients exposed to solvents more frequently developed: diffuse cutaneous SSc (P = .001), digital ulcers (P = .01), interstitial lung disease (P = .02), myocardial dysfunction (P = .04), and cancer (P = .003); in addition, these patients were more frequently anti-Scl 70 positive and anticentromere negative. Under multivariate analysis, significant factors for SSc associated with exposure to silica/solvents were: male gender (odds ratio 19.31, 95% confidence interval 15.34-69.86), cancer (odds ratio 5.97, 95% confidence interval 1.55-23.01), and digital ulcers (odds ratio 2.42, 95% confidence interval 1.05-5.56).

Limitations: The cohort originated from a single geographic region.

Conclusion: Occupational exposure to crystalline silica/solvents is correlated with more severe forms of SSc characterized by: diffuse cutaneous involvement, interstitial lung disease, general microangiopathy (digital ulcers and myocardial dysfunction), and association with cancer. Occupational exposure should be systematically checked in all patients with SSc, as exposed patients seem to develop more severe forms of SSc. (J Am Acad Dermatol 2015;72:456-64.)

Key words: cancer; crystalline silica; digital ulcers; interstitial lung disease; occupational factors; solvents; systemic sclerosis.

Systemic sclerosis (SSc) is an inflammatory disorder, of unknown origin, affecting the skin and other organs[1-3]; diffuse cutaneous SSc (dcSSc), interstitial lung disease (ILD), and pulmonary arterial hypertension have been associated with higher mortality in patients with SSc.[4-17]

Recently, a multicenter, case-control study showed that occupational exposure to crystalline

From the Department of Internal Medicine, Centre Hospitalier Universitaire (CHU) Rouen, and Institut National de la Santé et de la Recherche Biomédicale (INSERM) Unit 905, University of Rouen Institut Fédératif Multidisciplinaire sur les Peptides (IFRMP), Institute for Biochemical Research[a]; Departments of Biostatistics,[b] Dermatology,[c] Pneumology,[d] Occupational Medicine,[e] and Epidemiology,[f] CHU Rouen; Department of Dermatology, CHG Le Havre[g]; and Department of Internal Medicine, Centre Hospitalier Général (CHG) Elbeuf.[h]

Supported by a grant from the French Ministry of Health (PHRCIR 2003-0549), and sponsored by Rouen University Hospital (Etude TOSCAN, 2002-039-HP).

Conflicts of interest: None declared.

Accepted for publication November 24, 2014.

Reprint requests: Isabelle Marie, MD, PhD, Département de Médecine Interne, CHU de Rouen, 76031 Rouen Cedex, France. E-mail: isabelle.marie@chu-rouen.fr.

Published online January 10, 2015.

0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2014.11.027

silica/organic solvents has an impact on development of SSc.[2] Only a few series have compared the features of SSc in patients with and without exposure to crystalline silica/organic solvents.[8] This prospective study thus aims to compare the characteristics of SSc in patients with and without exposure to: (1) crystalline silica; and (2) organic solvents.

CAPSULE SUMMARY

- The features of patients with systemic sclerosis and occupational exposure to silica/organic solvents are poorly known.
- Occupational exposure to silica/solvents is correlated with more severe forms of systemic sclerosis characterized by: diffuse cutaneous involvement, interstitial lung disease, digital ulcers, myocardial dysfunction, and association with cancer.
- Occupational exposure should be systematically checked in all patients with systemic sclerosis.

METHODS

The study was approved by the institutional ethics committee review board (Comité de Protection des Personnes [CPP] de Haute-Normandie, France). Written informed consent was obtained from all patients.

Patients

Between 2005 and 2008, 142 patients with a definite diagnosis of SSc were included in the study. Criteria for diagnosis of SSc were based on the American College of Rheumatology preliminary classification.[9] There were 31 men and 111 women with a median age of 53 years. The median duration of the disease, from the onset of the first extra-Raynaud phenomenon organ clinical manifestation, was 4 years. Patients were grouped into disease subsets according to criteria by LeRoy et al[10]: dcSSc (n = 45) and limited cutaneous SSc (n = 97).

Assessment of exposure

Using a standardized questionnaire, patients were asked about occupational history of exposure to: crystalline silica and organic solvents (ie: white spirit, aromatic solvents, chlorinated solvents, and ketones). An expert committee (occupational physicians and epidemiologists), was formed retrospectively, for blind evaluation of occupational exposure to silica/solvents.[2,8]

Patients were also interviewed regarding their smoking habits; they were dichotomized into ever smokers (past smokers, current smokers) and never smokers.[11,12]

Assessment of SSc features

The following data were recorded: (1) first extra-Raynaud phenomenon organ clinical manifestation: sclerodactyly (bilateral skin thickening of the fingers),[13] digital ulcers, telangiectasis, arthralgia/arthritis, esophageal involvement, ILD, or pulmonary arterial hypertension; and (2) modified Rodnan score at inclusion.

Patients were also evaluated to detect systemic complications, including:

- digital ulcers and/or pitting scars;
- esophageal dysfunction based on findings from manometry—Hurwitz criteria for the degree of esophageal involvement was classified as severe (stage IV) and nonsevere (stages I/II/III) involvement[14];
- ILD was diagnosed if patients had: (1) restrictive changes (forced vital capacity [FVC] and vital capacity [VC] <80%) and diffuse capacity of carbon monoxide (DLCO) less than 70% by pulmonary function tests,[1] and (2) abnormalities consistent with ILD on high-resolution computed tomography scan of the lungs[1];
- left ventricular dysfunction[15] was defined as left ventricular ejection fraction less than 50% by echocardiography[16];
- pulmonary arterial hypertension was diagnosed if patients had a mean pulmonary arterial pressure of 25 mm Hg or higher with a pulmonary capillary wedge pressure of 15 mm Hg or lower on right heart catheterization[5];
- joint impairment;
- history of renal crisis.

Finally, 17 patients had cancer or history of cancer; in all cases, occupational exposure to silica/solvents preceded cancer onset. Overall 18 tumors developed in these 17 patients: breast (n = 4), lung (n = 3), bladder (n = 2), colon (n = 3), pancreas (n = 2), uterus (n = 2), esophagus (n = 1), and ovary (n = 1). Cancer onset preceded SSc diagnosis by 2 years (n = 4), was concurrently identified in association with SSc (n = 8), or developed within 3 years after SSc diagnosis (n = 6).

Patients underwent biochemical tests, ie: (1) erythrocyte sedimentation rate, C-reactive protein (mg/L), hemoglobin (g/dL); and (2) anti-topoisomerase I (anti-Scl 70), anticentromere, anti-RNA polymerase III, and anti-Th/To (nucleolar 7-2 and cytoplasmic 8-2 ribonucleoprotein) antibodies.