Silica-Associated Systemic Lupus Erythematosus in an Elderly Man

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Abstract

The predominantly young woman-orientated systemic lupus erythematosus (SLE) is a disease that involves an extremely complicated and multifactorial interaction of various genetic and environmental factors. Crystalline silica (Si) may act as an immunoadjuvant to increase secretions of inflammatory endogenous substances and antibody production. In addition, previous studies have suggested that exposure to Si may induce SLE. Although the biologic mechanism of Si in SLE is unclear, defective apoptosis leading to the prolonged survival of pathogenic lymphocytes was thought to be one of mechanisms of Si-associated SLE (sSLE). In the present study, a rare case of an elderly man suffering from sSLE responded well to glucocorticoid therapy. The present findings were reviewed with reference to previous literature.

Key words: autoimmune disease, lupus nephritis, silica, silicosis

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Introduction

The predominantly young woman-orientated systemic lupus erythematosus (SLE) is a disease that involves an extremely complicated and multifactorial interaction of various genetic, sex hormonal and environmental factors. Crystalline silica (Si) may act as an immunoadjuvant to increase secretions of inflammatory endogenous substances and antibody production. Recent findings have suggested that exposure to Si may be a risk factor for SLE induction. In the present study, we encountered an elderly Si-associated SLE (sSLE) man, who responded to glucocorticoid therapy with a favorable outcome.

Case Report

A 77-year-old man was admitted to our hospital for evaluation of general malaise and fever of unknown origin in July 2006. He had no serious past illnesses or relevant family history except for a short period of Si-exposure (he had worked for several months in a coal mine) and 30 years of smoking. Physical examination showed normal findings, except for high fever (39.0°C) and hemorrhagic scars on the right eyeground. Laboratory tests revealed normal leukocyte counts (4.76×10^3/mm^3) with lymphopenia (1.23×10^3/mm^3). C-reactive protein (CRP; 2.42 mg/dL), erythrocyte sedimentation rate (ESR; 32 mm/hr), anti-nuclear antibodies (ANA; 1/320; homogeneous pattern) and anti-double strand DNA antibodies (ds-DNA; 21 U/mL, normal <10) were elevated. Tests for anti-cardiolipin antibodies or lupus anticoagulant were negative. Urinalysis showed proteinuria (1.8 g/day) with hyaline and granular cylinders. Chest radiography portrayed small, rounded and diffused opacities with a few calcified nodules in bilateral lung images. High-resolution computed tomography of the lungs showed predominantly bilateral parenchymal micronodules in the posterior aspect of the upper zone with hilar-mediastinal lymphadenopathies (Fig. 1A-C). Gallium scintigraphy showed uniform accumulation of parenchymal micronodules in bilateral lungs with multiple areas of accumulation of aforementioned hilar-mediastinal lymph nodes without any signs in other organs. Tests of pulmonary function showed no spirometric abnormalities, except for reduced total lung capacity (4.45 L) and diffusing capacity of the lung for carbon monoxide (10.41 mL/min/mmHg). Broncho-alveolar lavage fluid (BALF) re-
Figure 1. Chest CT findings reveal fibrotic changes (arrowheads) with micronodules (arrows) preferentially in the posterior aspect of the bilateral upper lungs (Fig. 1A, C) and hilar-mediastinal lymphadenopathies (Fig. 1B: arrows).

Figure 2. Staining of the thoracoscopic biopsied right lung (S2) with the Hematoxylin and Eosin reagent (A: ×20; B: ×400). Silicotic nodules located in collagenous centers (*) with peripheral zone of dust-laden macrophages (arrowheads), lymphoid cells, birefringent silica particles by polarized light; symptoms consistent with silicosis. Some of lymphoid cells were plasmacytes (arrows).

Although histopathologically diagnosed as silicosis (Fig. 2A, B), direct Si-associated causative factors/events related to this disease were not noted, because neither respiratory symptoms nor symptomatic exacerbations were portrayed in chest radiography. Histological studies performed on the kidney under light microscopy revealed focal glomerulonephritis (Fig. 3A). IgG and C1q depositions on the basement membrane (Fig. 3C, D) and virus-like particles located within the endothelium (Fig. 3B) were observed with immunofluorescence and electron microscopy respectively. Those findings are consistent with lupus nephritis class III (A/C); active and chronic lesions of focal proliferative and sclerosing lupus nephritis defined by International Society of Nephrology/Renal Pathology Society 2003 classification. Bilateral pleurisy occurred thereafter (Fig. 4). He was diagnosed as having SLE based on the criteria (lymphopenia, ds-DNA, ANA, nephritis, pleurisy) defined by the American College of Rheumatology. On initiation of glucocorticoid therapy (methylprednisolone 1 g/day for 3 days followed by prednisolone 60 mg/day for a month) for a week, improvements in clinical symptoms, pleurisy and elevated ds-DNA titers were established. Glucocorticoid dosing has since then been tapered off gradually without recurrence (note; tapering was still in progress when this manuscript was written).

Discussion

SLE is a relatively rare disease. Although reliable data on SLE prevalence are limited, the incidence rate in the general population is estimated to range from 20 to 50 in 100,000. SLE, which is 10 times more commonly found in women than men, is especially predominant in women of childbearing age (1, 2). Although the exact pathoetiology of SLE remains elusive, it probably involves a complicated interaction of genetic, sex hormonal and environmental factors.
Since the report by Caplan (4) on the possible effects of Si on coal miners, occupational exposure to crystalline Si has been thought to be a possible risk factor for rheumatoid arthritis (RA); however, cases coincidental with sSLE have rarely been reported. Until the 1980s, evidence relating to sSLE in humans has been limited to a few case reports (5, 6). In the 1990s, cohort studies conducted in occupational groups demonstrated that exposure to high Si levels is associated with SLE (Table 1) (2, 7-11). Conrad et al (2) have found 28 confirmed SLE patients among 15,000 uranium miners exposed heavily to quartz dust with an estimated prevalence of 93: 100,000. According to their findings, characteristic clinical features of sSLE patients were manifested with a late onset (average age: 52.6; age range: 40-63 years); viz., a long latent period between exposure and onset (mean: 30.3; duration range: 11-50 years) with man dominance (all men) was observed. These features are consistent with our present findings and other reports, albeit contrary to idiopathic SLE (onset at late 30s with woman dominance) (12). Although the study by Sanchez-Roman et al (7) reported woman-dominant cases, their sample-population consisted predominantly of worker workers (44/ 50 workers) at a scouring powder factory. In a similar gender-orientated fashion, dominant sSLE prevalence in men might be attributed to the majority of workers being men (with Si-exposure risks) in the mining industry. Thus, specific bias (differences in population, exposure-assessment techniques, study designs, etc.) could affect any single study, and may complicate evaluation of the risks involved.

The lung lesions in the present case were diagnosed as silicosis, for silicotic nodules (dense lamellar collagenous centers, peripheral zones of dust-laden macrophages, lymphoid cells and birefringent silica particles by polarized microscopes).
light) were shown histopathologically (Fig. 2A, B). The diagnosis agreed with the radiographic findings, where nodules with fibrosis were preferentially located in the posterior aspect of the upper lungs, and the findings of slightly lymphocyte dominant BALF (8, 13). However, silicosis in the present case seems to be mild, because neither respiratory symptoms nor spirometric impairments were recognized and radiographic progression was categorized as not more than 1/1; i.e. mild profusion of silicosis according to the International Labor Organization international standard classification. It is reported that humoral immunologic abnormalities are not directly responsible for the lung changes in silicosis and can not be used as an index to predict the severity or progression of the autoimmune disease (14).

Although the biological mechanism of sSLE is unclear, certain immunosystemic abnormalities may be correlated with the onset; defective apoptosis leading to the prolonged survival of pathogenic lymphocytes is thought to be one of the sSLE mechanisms (15). Certain hypotheses have been proposed for this etiological perspective; (i) dysregulation of the Fas-Fas ligand (FasL) system and (ii) the adjuvant effect of defective macrophages.

In hypothesis (i), dysregulation of the Fas-mediated apoptosis pathway has been considered to play a role in autoimmune response; mutations of the Fas and FasL genes, which lead to defects in apoptosis, have been observed in autoimmune strains of mice; i.e. lpr mice for Fas and gld mice for FasL (16). They developed a syndrome that is serologically and pathologically similar to human SLE. In humans, the serum levels of soluble Fas (sFas), the most typical alternatively spliced variant of wild-type fas genes, are higher in silicosis and SLE patients (17, 18). It has been reported that the levels of serum sFas determined by enzyme-linked immunosorbent assay (ELISA) (using sFas ELISA kit; MBL, Nagoya, Japan) in silicosis patients (2.61±0.79 ng/mL, n=82, p<0.05; mean±s.d., number of patients, p value) and SLE patients (2.67±0.92 ng/mL, n=38, p<0.001) are significantly increased compared with those in healthy subjects (1.97±0.56 ng/mL, n=30) (19). In the present case, serum sFas was significantly increased (3.61 ng/mL) by the same technique. It is speculated that the sFas inhibits mFas-FasL binding through competition, preventing induction of apoptosis in lymphocytes (17).

Dysregulation of the Fas-FasL pathway might be also related to the development of silicosis. Si induces FasL expression through production of active oxygen in pulmonary macrophages in vitro and in vivo. And it has been speculated that FasL signaling induces inflammatory apoptosis in alveolar epithelial cells and macrophages with inflammatory cytokines, leading to silicosis (20, 21). The level of serum soluble FasL (sFasL), which is cleaved by matrix metalloprotease from membrane-bound FasL and determined by ELISA, is higher in the present case (0.31 ng/mL) than the previously reported value of healthy people (0.16±0.07 ng/mL, n=30) (19). As sFasL has similar physiological activity to FasL (18), elevation of sFasL may play a role in development of silicosis. The elevation of sFasL is observed as well in SLE patients, showing a positive correlation with sFas levels (19). The dysregulation of Fas-FasL pathway might not only be related to the onset of silicosis, but might be important also in the disruption of autoimmunity.

In hypothesis (ii), another nonspecific adjuvant effect of defective macrophages has been proposed. Si particles are thought not to be easily degraded by lysosomal enzymes and have various influences on the human body (22). Si added to antigen-stimulated lymphocyte cultures significantly increased the numbers of immunoglobulin-secreting cells in vitro (23), and silicosis patients in fact have an elevation of immunoglobulin (14). It is speculated that macrophages respond to Si by upregulating inflammatory cytokine production of tumor necrosis factor and interleukin-1, which in turn activate helper T-cells to facilitate B-cell production of antibodies. In other words, hyperactivated macrophages may then enhance the chronic inflammatory response to accelerate antibody production (22, 24, 25). The elevated values of serum zinc sulfate turbidity test (ZTT; 16.7 U, nor-
nal 2.3-12), thymol turbidity test (TTT; 23.0 U, normal 0.5-6.5), positive rheumatoid factor and sustained high fever may support such a chronic inflammatory state as in the present case. The findings of dust-laden macrophages and lymphoid cells with plasmocytes in the lung biopsy samples (Fig. 2A, B) support such inflammatory responses histopathologically. The presence of plasmocytes in silicosis lungs has never been documented, however, that particular finding in the present case may imply acceleration of the immune response to induce autoantibody production.

In addition, smoking habits of the patient might have accelerated SLE development. A recent meta-analysis provided evidence that susceptibility to SLE is associated with smoking (26). It is possible that DNA damage in smokers leads to ds-DNA autoantibody formation, and may play a role in the SLE development (27).

In summary, we encountered a rare case of sSLE-affected elderly man who responded to glucocorticoid therapy with a favorable outcome. Hitherto, cases with both silicosis and SLE have not been histopathologically established. In fact, to our knowledge, the present case study is the first report that provides evidence of the relevance of both diseases in humans. The exposure to Si-containing dust may predispose to SLE development, an event which has previously been described in RA. Although the exact pathoetiology of SLE remains elusive, persistent Si-exposure might lead to systemic immunological abnormalities. A more detailed pathogenesis of sSLE is warranted to clarify the relationship of Si with SLE. Furthermore, our present experience may remind physicians to take into account the occupational history (especially Si-exposure) of man patients diagnosed with SLE.

References