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Fever, Leukopenia and Autoantibody Complications in a Patient with Silicosis Successfully Treated with Prednisolone

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Abstract A 71 year-old-male was admitted to our hospital because of fever accompanied with leukopenia. He was initially treated with antibiotics, without success. He had worked as a stone mason since the age of 20 was diagnosed as having silicosis at the age of 30. A polyclonal increase of immunoglobulins and elevations of antinuclear factor, anti-DNA antibody, and rheumatoid factor were documented, but anti-topoisomerase I(anti-topo I) antibody and PR3- and MPO- antineutrophil cytoplasmic antibodies (ANCAs) were negative. HLA-DQB1 was *0301/*0502. Administration of prednisolone was effective for ameliorating fever and leukopenia. These results suggested the immunological pathogenesis for these symptoms with silicosis by interactions of silica, antigen presenting macrophages and T-cells through specific HLA, and stimulation of B-cells to produce autoantibodies.

Key words: fever, leukopenia, autoantibody, silicosis

Introduction

Silicon exposure has been associated with many different disorders, including pulmonary silicosis, emphysema, progressive systemic sclerosis (PSS), systemic lupus erythematosus (SLE), rheumatoid arthritis, dermatomyositis, glomerulonephritis, and vasculitis.[1)] Variously detected autoantibodies in patients with silicosis accompanied with autoimmune disorders have been immunoglobuins, anti-DNA antibody, antinuclear antibody, rheumatoid factor, immune complex, and anti-topoisomerase I (anti-topo I) antibody.[2-5)] The mechanism of the production of autoantibodies in these patients has been reported in association with specific HLA class II alleles.[4)5)]

We report a case of silicosis associated with leukopenia, fever, and various autoantibodies, successfully treated with the administration of prednisolone. These results suggested the immunological pathogenesis for these symptoms with silicosis.

Case report

A 71 year-old-male had complained of fever since September 2004. Leukopenia was diagnosed and he was referred to our hospital. He had had a history of silicosis since the age of 30 and mental depression at the age of 50. He had not the history of other diseases, and the family history was unremarkable. He had past history of smoking for 30 years. The patient had a fever of 39.4 ℃. Physical examinations revealed; anemia and jaundice were unremarkable, heart sounds were normal, normal vesicular sounds were audible in the lungs, and the liver and spleen were not palpable. The patient had no symptoms of PSS or other collagen disorders. Chest X-ray revealed emphysema with calcified nodules and small nodular lesions of the lungs (Fig. 1).

Computed tomography(CT) of the lungs revealed the same lesions. Vital capacity (VC) was 2.68 L(83.8% of expected value), and forced expiratory volume ($FEV_{1.0\%(G)}$) was 47.44% (73.5%). These findings were compatible with silicosis. Laboratory data on admission are shown in Table 1. Immunoglobulins were polyclonally increased. Autoantibodies for antinuclear antibody, anti-DNA antibody (double stranded), and rheumatoid factor were highly elevated. Anti-topoisomerase I (anti-topo I) antibody was negative. Soluble interleukin-2 receptor (sIL-2 R) was elevated. Antineutrophil cytoplasmic antibodies (PR3-ANCA and MPO-ANCA) were negative. HLA-DQB1 was *0301/*0502. Urinalysis revealed occult blood and proteinuria. Bacteriological and virological studies were negative. Administration of antibiotics was ineffective for fever. Administration of prednisolone, 30mg/day, was started, and the fever dropped thereafter, leukopenia was successfully treated (Fig. 2), and urinalysis became normal. Thereafter, the hematological findings remained normal, and the patient is currently alive and has been without any clinical manifestations for 2 years.

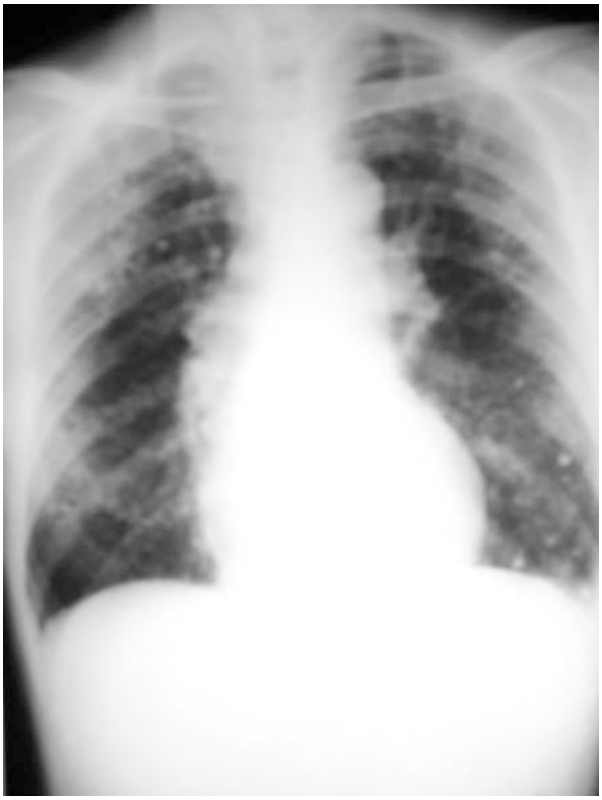

Fig. 1 Chest x-ray of the patient revealed emphysema with calcified nodules and small nodular lesions of the lungs, compatible with silicosis.

Discussion

In patients with silicosis, silicon-containing compounds have a pronounced adjuvant effect on the immune response. Silica is ingested by macrophages, which stimulates T- cells, and, in turn, stimulates B- cells to produce immunoglobulins and autoantibodies.[1)]

Table 1 Laboratory data on admission

RBC(x10^4/μL)	354	ANA	>1280,homogeneous
Ht(%)	30.5	anti-ds DNA(IU/ml)	>300
Hb(g/dl)	10.3	anti-Sm(U/ml)	7
Plt(x104/μl)	19.2	anti Topo I Ab	-
WBC(/μl)	800	RF(IU/ml)	71.2
N Band(%)	15	sIL-2 R(U/ml)	2240
N Seg(%)	30	PR3-ANCA(EU)	<10
Eo(%)	4	MPO-ANCA(EU)	<10
Ba(%)	1		
Ly(%)	30	Urinalysis	
Mono(%)	7	Red Cells(/HPF)	1-4
Atp Ly(%)	11	Protein(mg/dl)	122
Bone Marrow	Hypocellular		
CRP(mg/dl)	10.6		
Alb(g/dl)	2.4		
Glb(g/dl)	4.4		
IgG(mg/dl)	2650		
IgA(mg/dl)	211		
IgM(mg/dl)	100		

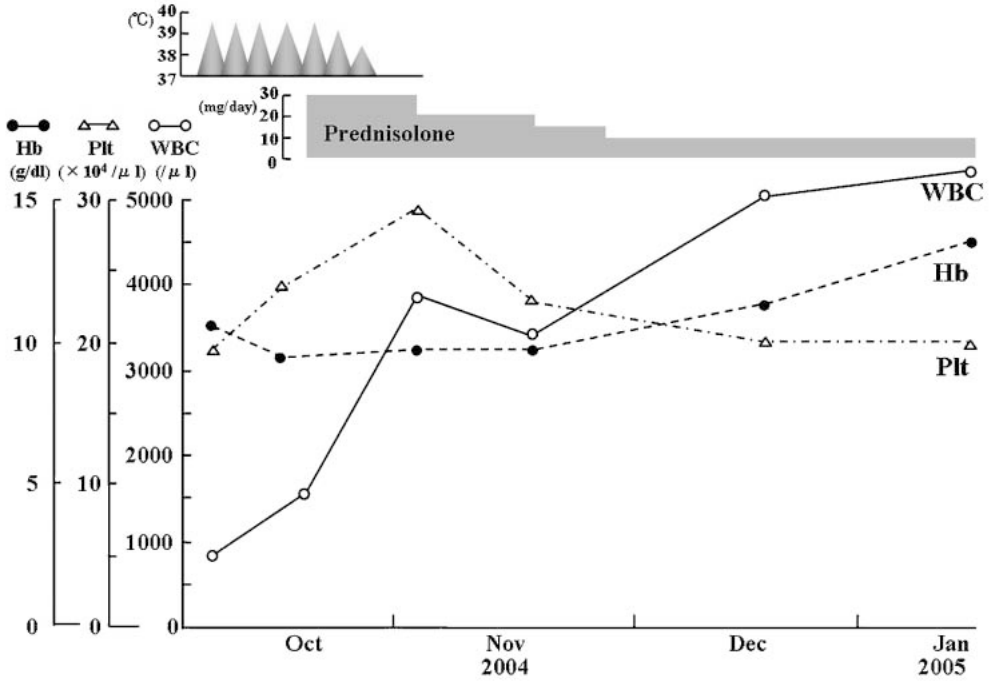

Fig. 2 Clinical course of the patient.

Silicosis is characterized by pulmonary fibrotic changes which consist primarily of an increase in collagen. Nagaoka et al. demonstrated higher levels of anti-human type I and type III collagen in silicosis patients.[2] They observed a correlation between anti-collagen antibodies and immunoglobulin G, and also demonstrated high values of anti-collagen antibodies in patients positive for antinuclear antibodies and rheumatoid factor. The measurement of these antibodies offers a useful index for evaluating the prognosis of pulmonary fibrosis and autoimmune abnormality in silicosis.[2]

In Japan, about 30 cases of silicosis accompanied with autoimmune diseases: 7 cases of PSS, 3 cases of SLE, 4 cases of autoimmune hemolytic anemia (AIHA), 2 cases of RA, 2 cases of polymyositis, a case of Wegener's granulomatosis, a case of Hashimoto disease, and 10 cases of adjuvant disease (including a case with AIHA); have been reported at 1992.[6] Elevations of polyclonal γ-globulin, especially IgG, and a high rate of positive autoantibodies such as antinuclear antibodies, anti-DNA antibodies, and rheumatoid factor, had been observed, as in the present patient.[6] Hematological changes were anemia and decreased lymphocyte blastogenesis.[6] The present patient had not been categorized with a specific autoimmune disease. Initially, the patient presented with leukopenia and fever, as rarely observed in autoimmune diseases such as SLE. These symptoms were easily ameliorated by the prednisolone administration.

Autoantibodies against topo-I have been reported to be specific to PSS, and can be used to identify subsets of patients with diffuse cutaneous involvement, pulmonary interstitial fibrosis, and peripheral vascular diseases.[4]

Kuwana et al. reported that either the DQB1* 0601 or * 0301 allele was recognized in all anti-topo I antibody-positive Japanese PSS patients.[4] Ueki et al. observed that among 81 patients with silicosis, anti-topo I antibody was positive in seven patients without any clinical features of autoimmune diseases such as PSS.[5] He also reported that the allelic frequency of HLA-DQB1 *0402 was significantly higher in anti-topo I-positive patients (28.6%) than in anti-topo I-negative patients (1.5%) or healthy controls (0.8%).[5] In addition, HLA-DQB1*0301, *0601, and DPB1 *1801 alleles were more frequently detected in anti-topo I-positive patients than in patients without anti-topo I or healthy volunteers, although a significant difference was not observed.[5] On the other hand, Horiki et al.

observed that DQB1*04 was shared by all of their five Japanese patients with anti-topo I autoantibodies in the overlapping syndrome of PSS and rheumatoid arthritis.[7] They concluded that the most important factor to induce anti-topo I autoantibodies seemed not be the type of alleles themselves, but the position of some specific amino acid residues in the DQB1 β domain.[4)5)] In the present patient, the HLA-DQB1 allele was 0301, anti-topo I was negative, and there was no clinical manifestation of PSS. Whether the association between the clinical manifestations of this patient and specific HLA allele, HLA-DQB1* 0301, is significant or not is unknown. Exposure to silicon-containing compounds has also been linked with ANCA-associated pauci-immune necrotizing cresentic glomerulonephritis and vasculitis.[1)] In the present patient, urinalysis initially revealed proteinuria and hematuria, but manifestations of glomerulonephritis or vasculitis were not observed, and PR3-ANCA and MPO-ANCA were negative. The urinalysis results became normal before discharge.

These abnormalities in the present patient support the immunological pathogenesis by the interactions of silica, antigen presenting macrophages and T-cells through specific HLA, and stimulation of B-cells to produce autoantibodies, and also suggest that diverse clinical manifestations related to various kinds of autoantibodies are seen in silicosis patients.

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