Notes

HIGH PREVALENCE OF ANTINUCLEAR ANTIBODIES IN SANDBLASTERS' SILICOSIS[1]

Summary

Of 39 silicotic sandblasters evaluated in 1972 and 1973, 17 (44 per cent) had positive serum antinuclear antibody reactions. This prevalence is higher than those reported for other pneumoconioses. Comparison of the groups positive and negative for antinuclear antibodies showed that patients positive for antinuclear antibodies were unlikely to have normal ventilatory function and were more likely to have roentgenograms showing large opacities. Both groups had similar proportions showing lobar cavitation or contraction.

In 1972 and 1973, we examined a number of sandblasters from the Louisiana Gulf Coast area and enrolled for study all of those with roentgenographic evidence of silicosis. Roentgenograms were read according to the ILO U/C classification (1) by 2 readers experienced in the use of this system. Criteria for selection included small rounded opacities of profusion grade of 1/1 or greater, involvement of both lungs, and nodulation remote from suspected tuberculous foci if present. The enrolled 39 patients thus constituted a consecutive series selected on the basis of occupational exposure and positive roentgenograms.

Stored frozen sera from these patients were tested at 1:10 dilution using a standard double immunofluorescence test for antinuclear antibody (ANA) (2). Rat liver was used as substrate and was treated with fluoresceine isocyanate conjugates of anti-human gamma globulin (Burroughs-Wellcome), containing both anti-IgG and anti-IgM, used in a dilution of 1:8.

Our results showed that 17 of these 39 men had positive ANA reactions at titers of 1:10 or greater. Comparison of the 17 ANA-positive and 22 ANA-negative men showed very similar mean ages (46.6 years versus 46.0), racial distributions (47 per cent black versus 45 per cent), and mean cigarette use (30.1 pack-years versus 28.2). The ANA-positive men had slightly lower average total years sandblasting (11.4 versus 13.2) and years sandblasting without external air supply (8.0 versus 8.7). Infectious granulomas were found in 2 of the 17 ANA-positive patients (one each with *Mycobacterium tuberculosis* and *M. kansasii*) and in 5 of the 22 ANA-negative patients (one each with *M. tuberculosis, M. intracellulare,* and *Cryptococcus species,* and 2 with *M. kansasii*). We concluded that the above factors did not determine which of our patients developed positive ANA reactions.

We then compared the ANA-positive and ANA-negative groups for differences in the distribution of roentgenographic changes. In one comparison, films were classified as showing (*1*) nodular silicosis with no large opacities, no contraction or cavitation ("simple" silicosis); (*2*) nodular silicosis with large opacities but no contraction or cavitation; or (*3*) nodular silicosis with contraction or cavitation. This classification, previously shown to correlate with functional impairments (3), showed similar distributions in the ANA-positive and ANA-negative groups (table 1). The rates of simple silicosis in both groups were comparable, although low because of the aggressive character of sandblasters' silicosis. A further comparison was made by classifying films only for the presence and size of large opacities (table 2). Note that the category "none" is not equivalent to "simple" silicosis, because it includes cases showing contraction or cavitation if they do not also show large opacities. In this comparison, significantly more of the ANA-positive patients had large opacities, and there was a trend showing a greater proportion of ANA reactivity for successively larger lesions; 4 of 5 patients with Type C opacities were ANA positive. Of patients with serial roentgenograms covering suitable intervals, the ANA-positive and ANA-negative patients showed similar rates of progression.

Lung function testing showed similar mean values for volumes, maximal expiratory flow rates, and carbon monoxide diffusing capacities in the 2 groups. Average annual changes were also not significantly different. When assessing patterns of disordered lung function in individual patients, however, only 1 of 17 (6 per cent) ANA-positive patients had normal lung function, whereas 7 of 22 (32 per cent) ANA-negative patients had normal function. In later studies from 29 patients with serial function tests, 2 of 14

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TABLE 1

DISTRIBUTIONS OF ROENTGENOGRAPHIC PATTERNS AMONG PATIENTS POSITIVE AND NEGATIVE FOR ANTINUCLEAR ANTIBODIES (ANA)

	Nodular Silicosis*		Nodular Silicosis with Large Opacities†		Nodular Silicosis with Contraction or Cavitation	
	(no.)	*(%)*	*(no.)*	*(%)*	*(no.)*	*(%)*
ANA positive (n = 17)	4	24	5	29	8	47
ANA negative (n = 22)	7	32	5	23	10	45

*No large opacities, no contraction or cavitation.
†No contraction or cavitation.

(14 per cent) ANA-positive patients were normal and 6 of 15 (40 per cent) ANA-negative patients were normal.

The 44 per cent ANA prevalence rate in this series exceeds rates reported for silicosis and other pneumoconioses. Twenty-five per cent of patients with clinical and roentgenographic evidence of asbestosis had ANA (2). Increased ANA prevalence has been found in coalworkers' pneumoconiosis (4), with a rate of 34 per cent reported by Lippmann and associates (5) (using mouse fibroblasts for nuclear substrate). Kang and co-workers (6) reported ANA in 8 of 31 (26 per cent) silicotics. In comparison, ANA prevalence in a random male sample was about 2 per cent (7) and was 3 per cent for healthy male control subjects (of comparable age) tested in our laboratory using techniques identical with those used in the present study. A 2.6 per cent rate was observed in male asbestos workers (mean age, 54 years) with normal roentgenograms and no clinical evidence of asbestosis. An ANA prevalence of 18 per cent was reported in patients with severe chronic bronchitis (8).

Careful methods are important in immunofluorescent antibody tests. Mouse liver is among the less sensitive substrates for detection of ANA. Low test sensitivity, minimizing "false positives," is important in interpreting prevalence rates that are high compared with those in other series. Another type of false positive results from over-reading of fluorescence. The intra-observer error of reproducibility of the reader (MTW) of the present series has been assessed; the rate of false positive reading, i.e., 1 positive to 3 negative, when the same sample was read on 4 occasions in a randomized study, was 2 per cent. Inter-observer variability was tested by exchange of serum samples with an independent reader, and there was 84 per cent agreement on 126 sera.

TABLE 2

COMPARISON OF PRESENCE AND SIZE OF LARGE OPACITIES IN PATIENTS POSITIVE AND NEGATIVE FOR ANTINUCLEAR ANTIBODIES (ANA)

		Size (According to ILO U/C Classification)*		
	None	A	B	C
ANA positive (n = 17)	5†	2	6	4
ANA negative (n = 22)	13†	5	3	1

*A = aggregate diameter $\leq$ 5 cm; B = aggregate diameter $\leq$ one-third of area of right lung; C = aggregate diameter > one-third of area of right lung.
†$\chi^2 = 3.43$, $0.025 < P < 0.05$ for a one-tailed test.

* * *

The present series contributes to a growing appreciation of high ANA prevalence rates in pneumoconioses. Silicosis, and coalworkers' pneumoconiosis with progressive massive fibrosis, show particularly high rates. In our series, ANA reactivity is related to the presence of large opacities and is further correlated with the larger sizes of these opacities. It is not correlated with the development of upper lobe contraction or cavitation, suggesting that those changes may be produced by a different mechanism. Caution should be exercised in applying the term "progressive massive fibrosis," which may include cases showing large opacities ("massive") and others showing lobar contraction ("fibrosis").

Immune reactions may play a role in the pathogenesis of lung fibrosis in silicosis. Immunoglobulins (9) and immunoglobulin-secreting cells (10) are present in and around silicotic nodules, and autoimmune diseases occasionally complicate silicosis (11, 12). Although the cytotoxic effect of silica is rapid and chemically mediated, the subsequent events in the formation of fibrosis and the eventual course of clinical changes provide many potential loci for immunologic influence. Even if autoimmunity is ultimately shown to play a peripheral role in silicosis, the relationship provides an opportunity to explore more general aspects of autoimmunity.

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OBSERVATIONS OF THE PATHOLOGY OF CLUBBED FINGERS WITH SPECIAL REFERENCE TO MAST CELLS

Summary

Mast cell counts were made, in tissue samples of normal and clubbed fingers obtained at autopsy, to investigate the possibility that mast cells act as an intermediary in the development of finger clubbing. Quantitative measurements of the composition of the tissues of the normal and clubbed nail bed were also made.

The only significant difference in mast cell numbers in clubbed fingers was a decrease in mast cells in the tissues just superficial to the nail. The appearance of the mast cells was normal. The portion of blood vessels and other tissues was not significantly different from normal.

Many theories have been proposed to explain finger clubbing, but none is capable of explaining the development of clubbing in all the varied conditions in which it occurs. Theories involving a vasodilator hormone, normally removed by the pulmonary circulation, are particularly attractive in clubbing that develops with shunts of venous blood through the lungs or secondary to a carcinoma of the lung that may produce a vasodilating hormone. Such theories are less able to explain clubbing that occurs in bacterial endocarditis, tumors of the pleura and esophagus, or colonic disease. The vagus nerve plays a certain, but undefined, role in finger clubbing and hypertrophic osteoarthropathy (1).

The present study was carried out to investigate the possible intermediate role of mast cells in finger clubbing. Selye (2) has reviewed the evidence that has been put forward to link mast cells with the formation of collagen, ground substance, and hyaluronic acid. The finger blood flow is increased in clubbing (3), although probably not in hypertrophic osteoarthropathy (4, 5). Mast cells are often distributed in, or close to, the walls of small blood vessels, and by the liberation of histamine they may exert an effect on blood flow and permeability of the small vessels.

In some species, e.g., the rat, mast cells are more

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