

Asbestosis and probable microscopic polyangiitis

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Several inorganic dust lung diseases (pneumoconioses) are associated with autoimmune diseases. Although autoimmune serological abnormalities are common in asbestosis, clinical autoimmune/collagen vascular diseases are not commonly reported. A case of pulmonary asbestosis complicated by perinuclear-antineutrophil cytoplasmic antibody (myeloperoxidase) positive probable microscopic polyangiitis (glomerulonephritis, pericarditis, alveolitis, multineuritis multiplex) is described and the possible immunological mechanisms whereby asbestosis fibres might be relevant in induction of antineutrophil cytoplasmic antibodies are reviewed in the present report.

Key Words: *Primary care; Screening; Spirometry*

Pulmonary diseases caused by the inhalation of inorganic dusts, pneumoconioses, are associated with systemic autoimmune diseases, the so-called collagen vascular disorders. The best recognized example is the coexistence of rheumatoid arthritis and coal-workers pneumoconiosis, referred to as Caplan's syndrome (1). There is also a higher prevalence of connective tissue disorders (rheumatoid arthritis, systemic lupus erythematosus, scleroderma, etc) in patients with silicosis (2). There is an increase in prevalence of autoantibodies in subjects with asbestosis (3) and there has been speculation that autoantibodies might play a role in the pathogenesis of asbestosis and other connective tissue disorders (4). However, there are few reports of asbestosis associated with overt connective tissue disorders. We report a case of asbestosis associated with perinuclear-antineutrophil cytoplasmic antibodies (p-ANCA) (myeloperoxidase [MPO]) positive systemic connective tissue disease suspected of being a microscopic polyangiitis.

CASE PRESENTATION

Our patient was a 63-year-old male retired construction worker when he presented with his acute illness in September 1996 in Vancouver. He had moderate to marked asbestos exposure history over his 40 years in the construction trade, more so during the earlier half of this occupation. Although he had no antecedent lung symptoms, chest radiographs performed in the early 1990s in British Columbia showed mild peripheral basilar reticular interstitial disease with bilateral calcified pleural

Amiantose et polyangéite microscopique probable

Plusieurs pneumopathies (pneumoconioses) liées aux poussières inorganiques sont associées à des maladies auto-immunes. Même si les anomalies sérologiques auto-immunes sont fréquentes dans l'amiantose, la documentation fait rarement état de maladies auto-immunes ou de collagénose avec manifestations cardiovasculaires décelables cliniquement. Voici un cas d'amiantose pulmonaire, compliquée d'une polyangéite (glomérulonéphrite, péricardite, alvéolite, polynévrite) microscopique probable à anticorps cytoplasmiques antineutrophiles périnucléaires (myéloperoxydase). Il sera également question de mécanismes immunitaires possibles mis en cause dans le rôle des fibres d'amiante dans l'induction des anticorps cytoplasmiques antineutrophiles.

plaques; these were interpreted as evidence of (mild) asbestosis and benign asbestos pleural disease. A representative chest radiograph is shown in Figure 1. The only additional history was a brief, transient episode of colitis, apparently associated with a normal barium enema study many years earlier. The patient had had no symptoms nor treatment for this condition for 25 to 30 years.

In September 1996, he presented with a two-month history of progressive dyspnea and cough, and a several-day history of severe retrosternal sharp chest pain relieved only by sitting forward. The relevant clinical findings at that time were reported to include notable bilateral basal inspiratory crackles and a pericardial friction rub. Investigations were as follows. Hematology was normal except for a marked elevation of erythrocyte sedimentation rate (82 mm/h). Electrolytes and other chemistries were normal other than a rise in his serum creatinine from 100 µmol/L to 150 µmol/L. Urinalysis revealed microscopic hematuria and red blood cell casts, along with proteinuria. Chest radiograph revealed previous asbestosis changes, but also showed increased ground glass opacification throughout, but more prominent in the bases, suggesting active alveolitis. Pulmonary function showed severe restriction (total lung capacity 43%, forced vital capacity 41%, forced expiratory volume in the first second 57%, diffusing capacity of the lung for carbon monoxide 54%). An electrocardiogram revealed changes 'consistent with pericarditis'. An echocardiogram showed a small pericardial effusion. Immunological blood work demonstrated negative antinuclear antibody, negative

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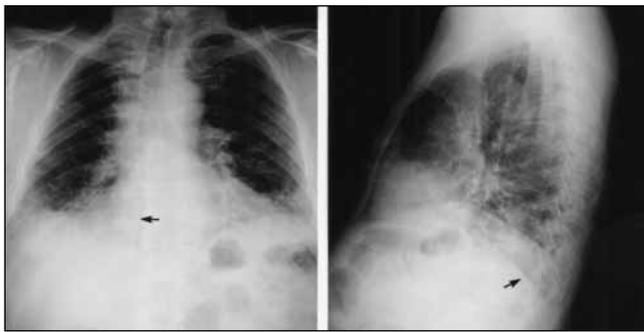


Figure 1) Posteroanterior and lateral chest radiograph demonstrating the peripheral and basilar interstitial lung disease. Calcified pleural plaques are visible faintly adjacent to the left hemidiaphragm on the lateral and right medial pleural on the posteroanterior (arrows)

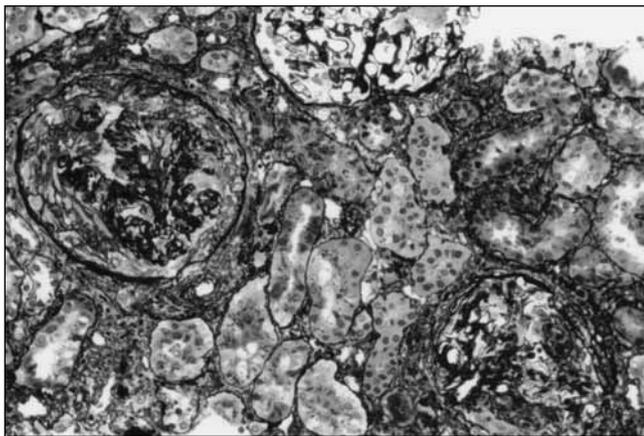


Figure 2) Photomicrograph from the renal biopsy in 1996 showing three glomeruli and intervening tubules. The glomerulus at the upper central part of the picture is normal. The other two glomeruli show large cellular crescents with partially destroyed and compressed tufts (methenamine silver stain, 200× magnification)

rheumatoid factor and positive p-ANCA in an MPO pattern. A percutaneous renal biopsy was done. There was a focal segmental (three glomeruli of 20) necrotizing glomerulonephritis with associated crescents seen in two glomeruli (Figure 2). No vasculitis was identified on the renal biopsy. The final report was that of a pauci-immune focal segmental crescentic glomerulonephritis of uncertain etiology. With the combination of p-ANCA (MPO type) positive glomerulonephritis, pericarditis and acute alveolitis (superimposed on chronic asbestosis changes), the presumptive diagnosis of microscopic polyangiitis was made. Prednisone, at 60 mg/day, was prescribed and within a week there was marked resolution of both symptoms and signs. The chest pain, pericardial rub and the majority of the inspiratory crackles resolved. Serum creatinine fell to less than 100 µmol/L, the active urinary sediment resolved, and both the chest radiograph and pulmonary function improved but did not normalize. Follow-up lung function revealed mild restrictive changes (total lung capacity 68%, forced vital capacity 69%, forced expiratory volume in the first second 85% and diffusing capacity of the lung for carbon monoxide 74%). At this time, cyclophosphamide 75 mg/day (approximately 1 mg/kg) was added.

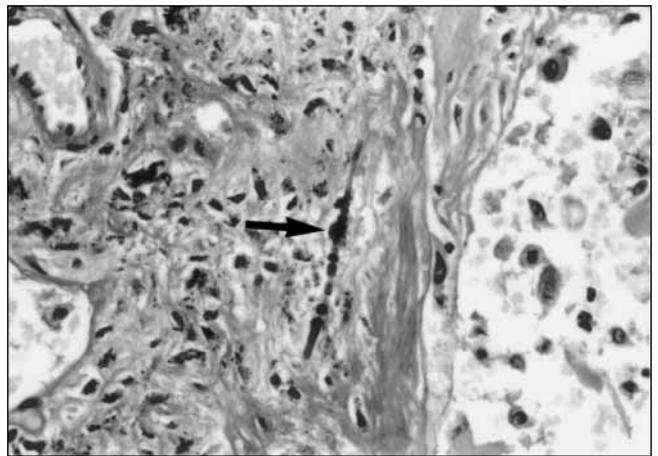


Figure 3) Ferruginous (asbestos) body (shown by arrow) showing characteristic beaded appearance with clubbing at either end and faintly lucent core lying within dense interstitial fibrous tissue of lung; autopsy specimen 2001 (hematoxylin and eosin stain, 200× magnification)

The patient continued to do well on prednisone 10 mg/day to 15 mg/day and cyclophosphamide 75 mg/day and moved back to Saskatchewan in 1997 where he resided for four years until his death. In September 1997, he developed multineuritis multiplex, primarily involving weakness of the right arm and ptosis of the right eye. This was thought to be a component of his p-ANCA positive connective tissue disorder, thus, he received a brief course of high dose intravenous methyl prednisolone and symptoms resolved.

Over the next four years, the patient was on variable dose prednisone at around 15 mg/day to 20 mg/day. Renal, pericardial and neurological disease did not flare. The prednisone dose was adjusted primarily based on lung symptoms (predominantly cough and slight dyspnea) and (sometimes subtle) changes in lung function. Over the four years, there was a gradual worsening of the restrictive disease. Cyclophosphamide was maintained in the range of 75 mg/day to 100 mg/day. In late 2001, hematuria developed likely as a complication of cyclophosphamide and this drug was switched to chlorambucil at a dosage of 2 mg/day.

In December 2001, he was admitted to hospital with increased cough, dyspnea and respiratory failure. Chest radiograph revealed the presence of chronic interstitial lung disease and some subtle airspace disease. He had a fever (38°C) and a macular rash over his chest. A radionuclide lung scan and a helical computerized tomographic scan suggested pulmonary thromboembolic disease. Unfortunately, no definitive antimortem diagnosis was made. In addition to a more intensive treatment for collagen vascular disease (high dose intravenous methylprednisolone with oral chlorambucil), he received treatment for pulmonary thromboembolic disease, conventional respiratory tract infection and opportunistic infection. He continued to deteriorate and staphylococcal septicemia was identified shortly before death.

An autopsy confirmed marked changes of asbestosis with numerous ferruginous (asbestos) bodies (Figure 3). The major cause of death was disseminated fungal disease throughout all organs, including the lung and kidneys. No active vasculitis was found postmortem.

DISCUSSION

Our patient had definite clinical and autopsy evidence of asbestosis and benign asbestos calcified pleural plaques. This was complicated by a p-ANCA (MPO) positive systemic collagen vascular disorder (glomerulonephritis, pericarditis, alveolitis and multineuritis). No definite vasculitis was identified on renal biopsy or autopsy and neither angiography nor further biopsies were indicated. However, the clinical and serological picture suggested a systemic vasculitis, probably microscopic polyangiitis (5). The absence of vasculitis at autopsy is not surprising since prednisone and cyclophosphamide had been given continuously for five years and a higher dose of parenteral methyl prednisolone along with chlorambucil had been given for four weeks before his death.

Ulcerative colitis, which our patient may have had 30 years earlier, is associated with p-ANCA which does not react with MPO (6). The colitis-associated p-ANCA is thus, different than the vasculitis-associated p-ANCA (6). Because of the MPO specificity and the remoteness of the colitis, we feel that our patient's ANCA was not due to his colitis.

The relation between immunological abnormalities and asbestos exposure has been established. As early as 1965, Pernis et al (7) noticed the higher incidence of rheumatoid factor in patients with asbestosis. In 1970, Turner-Warwick and Parkes (8) found antinuclear antibodies in the sera of asbestosis patients. In 1974, Lange (9) also noticed hypergammaglobulinemia in the sera of these patients.

In 1979, Lange (10) hypothesized that rheumatoid factor accompanies or is involved in the lung fibrotic process, yet the mechanism of the autoantibody production was not clear. Miller et al (11) in 1979 thought that antibody production could be an effect of a normal immune response to tissue autoantigens modified by asbestos. Lange (10) also reported the presence of antismooth muscle antibodies in asbestos workers, especially if they suffered chronic inflammation of the upper respiratory tract and bronchi.

Increased serum concentrations of immunoglobulin (Ig) E, IgA, and IgM have been seen in asbestos workers (8) and immune complexes have been suggested to play a role in the pathogenesis of the interstitial inflammatory reactions in the lung (3). Elevation of antinuclear antibodies, immune complexes and immunoglobulin levels suggest B lymphocyte hyperactivity, which could be the result of polyclonal B cell stimulation, mediated either by asbestos fibers themselves or degradation products released from asbestos-macrophage interaction (4). Similar mechanisms may cause depression of the T lymphocyte suppressor cell system with subsequent B cell overactivity (12). Kang et al (13) have suggested impairment in T lymphocyte function. Some studies measuring T-cells in asbestosis have reported a decrease in both their percentage and absolute numbers in the circulation (14). Both systems (T suppressor cell and B cell) may contribute to the humeral abnormalities in asbestos exposed workers (4).

Interestingly, within a three-year period after a Japanese earthquake, there was a noticeable increase in ANCA-related angitis. The investigators hypothesized that substances in the environment might have bound to the cytoplasmic MPO leading to modified self-determinant inducing autoimmunity to MPO. Asbestos particles in the air increased more than 20 times

for 30 months after this earthquake, raising speculation of a possible causal role (15). On the other hand, some investigators claimed that the activation of alveolar macrophage by asbestos is the inciting event of asbestosis immunopathogenesis due to the release of lysosomal enzymes, fibrogenic factors, lymphokines and chemotactic factors which could lead to over activity of the B cell system and relaxation of the T cell surveillance (4). The resident alveolar macrophages can modulate the immunological response by presenting the processed antigen (eg, asbestos fibers) to the circulating lymphocytes (16).

Microscopic polyangiitis is a vasculitis which primarily affects capillaries, venules or arterioles. Involvement of small and medium sized arteries may also be present. Both Wegener's granulomatosis and microscopic polyangiitis are associated with the presence of ANCA and similar histological changes. They are thought to be part of a clinical spectrum. ANCA in Wegener's granulomatosis is directed against proteinase 3 (c-ANCA) in contrast to microscopic polyangiitis in which ANCA most commonly reacts against MPO (p-ANCA) and less often against proteinase 3 (17,18). Polyangiitis presents with similar microscopic renal lesions to Wegener's granulomatosis, as well as similar nondiagnostic systemic symptoms and classic respiratory tract lesions (19).

The initiating events leading to the initiation of ANCA are uncertain but may include infections, genetic or environmental factors. The frequency of respiratory tract involvement suggest that exposure to an inhalational agent may be a possible inciting event. For example, subjects with ANCA-associated vasculitis are 4.4 times more likely to have a history of silica dust exposure (20).

ANCA may be epiphenomena related to another pathological process (21) or they may be antibodies directed against newly exposed epitopes of the target autoantigen. The degree of antibodies production will depend on the help of the T cell (22). It has been shown that subjects with ANCA positivity have higher levels of CD₄ T positive cells and monocytic activation markers (such as interleukin-12). Consequently, these mediators are a major inducer of TH₁ cytokines such as TNF- α and interferon gamma that induce a process in neutrophils called 'priming' in which neutrophils express on their surface the unexposed cytosolic proteinase 3 and MPO making them accessible to antibodies attack, leading to degranulation and tissue damage (23).

The patient presented here had remote exposure to asbestosis, years later he presented with nonspecific respiratory symptoms, pericarditis, renal insufficiency and active urine sediment secondary to glomerulonephritis. Based on the different hypotheses we presented, his disease can be explained by the possible interaction between the asbestos fibers and the engulfing macrophages leading to the release of cytokines which could have primed the neutrophils to express MPO on the surface, exposing it to self-reacting antibodies. These autoantibodies could have been created in response to modified self-determinants which resulted from macrophages binding with asbestos fibers (ie, to MPO). This reaction could have started and perpetuated the ANCA-induced microscopic polyangiitis in asbestos-exposed patients.

Despite the common appearance of autoantibodies in subjects with asbestosis, there are few reports of clinical coexistent

collagen vascular disease. Bartsch et al (24) have reported a case of systemic lupus erythematosus in asbestosis. Despite the interesting association of postearthquake ANCA-positive vasculitis and increased atmospheric asbestos particles (15), we believe this is the first reported observation of microscopic polyangiitis complicating asbestosis.

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REFERENCES

1. Caplan A. Certain unusual radiological appearances in the chest of coal-miners suffering from rheumatoid arthritis. *Thorax* 1953;8:29-37.
2. Rosenman KD, Moore-Fuller M, Reilly MJ. Connective tissue disease and silicosis. *Am J Ind Med* 1999;35:375-81.
3. Doll NJ, Diem JE, Jones RN, et al. Humoral immunologic abnormalities in workers exposed to asbestos cement dust. *J Allergy Clin Immunol* 1983;72:509-12.
4. Doll NJ, Stankus RP, Barkman HW. Immunopathogenesis of asbestosis, silicosis, and coal workers' pneumoconiosis. *Clin Chest Med* 1983;4:3-14.
5. Jayne D, Rasmussen N, Andrassy K, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Engl J Med* 2003;349:36-44.
6. Saxon A, Shanahan F, Landers C, Ganz T, Targan S. A distinct subset of antineutrophil cytoplasmic antibodies is associated with inflammatory bowel disease. *J Allergy Clin Immunol* 1990;86:202-10.
7. Pernis B, Vigliani EC, Selikoff IJ. Rheumatoid factor in serum of individuals exposed to asbestos. *Ann N Y Acad Sci* 1965;132:112-20.
8. Turner-Warwick M, Parkes WR. Circulating rheumatoid and antinuclear factors in asbestos workers. *Br Med J* 1970;3:492-5.
9. Lange A. An epidemiological survey of immunological abnormalities in asbestos workers. II. Serum immunoglobulins levels. *Environ Res* 1980;22:176-83.
10. Lange A. An epidemiological survey of immunological abnormalities in asbestos workers. I. Nonorgan and organ-specific autoantibodies. *Environ Res* 1980;22:162-75.
11. Miller K, Weintraub Z, Kagan E. Manifestations of cellular immunity in the rat after prolonged asbestos inhalation. I. Physical interactions between alveolar macrophages and splenic lymphocytes. *J Immunol* 1979;123:1029-38.
12. Gaumer HR, Doll NJ, Kaimal J, Schuyler M, Salvaggio JE. Diminished suppressor cell function in patients with asbestosis. *Clin Exp Immunol* 1981;44:108-16.
13. Kang K, Sera Y, Okochi T, Yamamura Y. Letter: T lymphocytes in asbestosis. *N Engl J Med* 1974;291:735-6.
14. Morris DL, Greenberg SD, Lawrence EC. Immune responses in asbestos-exposed individuals. *Chest* 1985;87:278-80.
15. Yashiro M, Muso E, Itoh-Ihara T, et al. Significantly high regional morbidity of MPO-ANCA-related angitis and/or nephritis with respiratory tract involvement after the 1995 great earthquake in Kobe (Japan). *Am J Kidney Dis* 2000;35:889-95.
16. Hartmann DP. Immunological consequences of asbestos exposure. *Surv Immunol Res* 1985;4:65-8.
17. Hoffman GS, Kerr GS, Leavitt RY, et al. Wegener granulomatosis: An analysis of 158 patients. *Ann Intern Med* 1992;116:488-98.
18. Rose BD, King TE, Jr., Hoffman GS. Clinical manifestations and diagnosis of Wegener's granulomatosis and microscopic polyangiitis. *UpToDate* 2003;11(2).
19. Woodworth TG, Abuelo JG, Austin HA 3rd, Esparza A. Severe glomerulonephritis with late emergence of classic Wegener's granulomatosis. Report of 4 cases and review of the literature. *Medicine (Baltimore)* 1987;66:181-91.
20. Hogan SL, Slatterly KK, Dooley MA, Nachman PH, Jeanette JC, Falk R; Glomerular Disease Collaborative Network. Silica exposure in anti-neutrophil cytoplasmic autoantibody-associated glomerulonephritis and lupus nephritis. *J Am Soc Nephrol* 2001;12:134-42.
21. Kallenberg CG, Brouwer E, Weening JJ, Tervaert JW. Anti-neutrophil cytoplasmic antibodies: Current diagnostic and pathophysiological potential. *Kidney Int* 1994;46:1-15.
22. Johnson RJ. The mystery of the antineutrophil cytoplasmic antibodies. *Am J Kidney Dis* 1995;26:57-61.
23. Jennette JC. Pathogenic potential of anti-neutrophil cytoplasmic autoantibodies. *Lab Invest* 1994;70:135-7.
24. Bartsch P, Salmon J, Mahieu P. Asbestosis and systemic lupus erythematosus. *Int Archs Allergy Appl Immunol* 1980;61:28-31.



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