Proposed Criteria for Mixed-Dust Pneumoconiosis: Definition, Descriptions, and Guidelines for Pathologic Diagnosis and Clinical Correlation

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We defined mixed-dust pneumoconiosis (MDP) pathologically as a pneumoconiosis showing dust macules or mixed-dust fibrotic nodules (MDF), with or without silicotic nodules (SN), in an individual with a history of exposure to mixed dust. We defined the latter arbitrarily as a mixture of crystalline silica and nonfibrous silicates. According to our definition of MDP, therefore, MDF should outnumber SN in the lung to make a pathologic diagnosis of MDP. In the absence of confirmation of exposure, mineralogic analyses can be used to support the pathologic diagnosis. The clinical diagnosis of MDP requires the exclusion of other well-defined pneumoconioses, including asbestosis, coal workers' pneumoconiosis, silicosis, hematite miners' pneumoconiosis, welders' pneumoconiosis, berylliosis, hard metal disease, silicate pneumoconiosis, diatomaceous earth pneumoconiosis, carborundum pneumoconiosis, and corundum pneumoconiosis. Typical occupations associated with the diagnosis of MDP include metal miners, quarry workers, foundry workers, pottery and ceramics workers, and stonemasons. Irregular opacities are the major radiographic findings in MDP (ILO 1980), in contrast to silicosis, in which small rounded opacities predominate. Clinical symptoms of MDP are nonspecific. MDP must be distinguished from a variety of nonoccupational interstitial pulmonary disorders. HUM PATHOL 35:1515-1523. © 2004 Elsevier Inc. All rights reserved.

Key words: **dust, pneumoconiosis, silica, silicates, silicosis.**

Abbreviations: **MDP, mixed-dust pneumoconiosis; MDF, mixed-dust fibrotic lesions; SN, silicotic nodules.**

Cases of pneumoconiosis that do not show typical clinicopathologic features of silicosis or other well-defined pneumoconiosis are frequently encountered in Japan and elsewhere. The term *mixed-dust pneumoconiosis* (MDP) originated in European countries to describe the lung lesions of ferrous and nonferrous foundry workers[1-3] where concomitant exposure to silica and nonfibrogenic dusts occurred. However, some confusion and ambiguity remain in terms of its definition. The purpose of this consensus report is to arrive at a practical working definition for MDP that encompasses a majority of cases. Here we have chosen arbitrarily to

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An outline of this consensus was presented at the 6th International Conference on Environmental & Occupational Lung Disease at Vancouver, British Columbia, Canada (February 11-14, 1999).

The NIKKO-Symposium on Mixed-Dust Pneumoconiosis was held October 18-19, 1997, in Nikko, Tochigi, Japan, to develop diagnostic criteria for mixed-dust pneumoconiosis under the auspices of Labour Welfare Corporation, Tokyo, Japan. The Organizing Committee included Keizo Chiyotani, Koichi Honma, Yutaka Hosoda, and Hisao Shida, and participants included Zoltán Adamis, Eduardo Algranti, Toshiharu Fuyuki, Kiyonobu Kimura, Otha Linton, Michihito Mishina, Hiroshi Morikubo, Alvaro R. Osornio-Vargas, Yoshiaki Saitoh, Yasushi Shinohara, and Hiroshi Watanabe.

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0046-8177/$—see front matter

doi:10.1016/j.humpath.2004.09.008

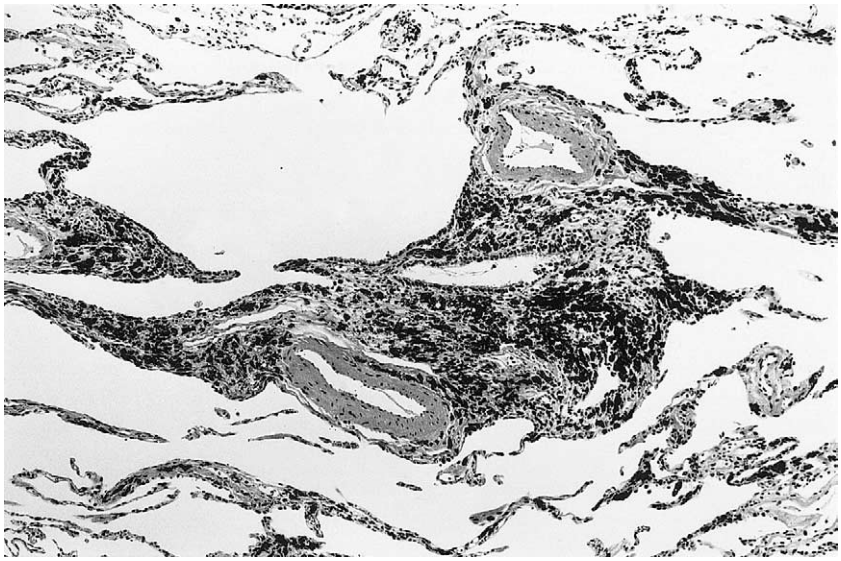

FIGURE 1. Histology of dust macules, showing peribronchiolar and perivascular collection of dust-laden macrophages accompanied by little collagen fibrosis. A mild centrilobular emphysema is seen. Hematoxylin & eosin; original magnification, ×25.2.

focus on a narrow definition of MDP, based on the pathologic descriptions of the lungs of patients exposed occupationally to a mixture of crystalline silica and mainly, nonfibrous silicates. Silicates represent relatively weakly fibrogenic dusts and modify the intense fibrogenic response to crystalline silica, as do other dusts such as iron.[4] Iron oxide and non-coal carbon particles are considered to be minor constituents of mixed dust in certain situations. Crystalline silica plays a key role in our definition of MDP, and it is expected that this definition would constitute the basis for further attempts to evaluate diverse biologic effects of combinations of *nonsiliceous* dust mixture in general.[5]

HISTORICAL REMARKS AND EXPERIMENTAL BACKGROUNDS

In 1934, Stewart and Faulds[6] reported the clinicopathologic and mineralogic features of lung changes in 15 hematite miners; these features closely resemble those of mixed-dust fibrosis. Stewart and Faulds[6] categorized it as "sidero-silicosis" at that time. The term *mixed-dust pneumoconiosis* (Mischstaubpneumokoniose) was first introduced by Uehlinger in 1946.[1] According to his clinicopathologic descriptions of MDP, "mixed dust granulomas" are softer than those of the silicotic lesion, and the fibrosis of silicotic type is masked extensively by the mixture of dust. Persistent layering of the granuloma with paucicellular fibrosis alternating with histiocyte-rich, less fibrotic tissue, prominent vasculature, and microcavitation further were considered to be characteristic of MDP pathology. The evolution of clinical symptoms in MDP was slower than that of those of silicosis because of the less prominent lung fibrosis. Rapidly progressive pulmonary tuberculosis was also seen but less often than in silicosis.

Several years later, Harding et al[2] described perivascular and peribronchial reticulin and collagen fibrosis ("dust reticulation") as a cardinal feature of MDP. The lesions that they described showed, in most instances, intermediate features between dust macules and mixed-dust fibrosis. Exposure to mixed dust that contained a small proportion of free silica was considered to be responsible for the development of MDP. Regarding the threshold level, a mixture of about 10% free silica was mentioned by McLaughlin,[7] and later, of <18% by Nagelschmidt.[8] In the German literature, the term *mixed-dust silicosis* (Mischstaubsilikose) was preferentially used instead of *mixed-dust pneumoconiosis*.[9,10] The term *anthracosilicosis* was often used when the nonsiliceous component included carbon (mostly coal).[11,12]

Early descriptions of the chest radiograph findings ranged from mottling[6] or snowflake picture[9] to reticulation.[2,7] Di Biasi[9] pointed out difficulties in differentiating mixed-dust silicosis from tuberculosis on the roentgenograms.

A number of experimental studies have been performed so far, focusing on the biologic effect of mixed dust that is composed of both crystalline silica and nonsiliceous particles. The results indicate that the intense fibrogenic effect of crystalline silica is modified or dampened by a variety of agents including iron,[13-16] coal,[17,18] feldspar,[16] kaolin,[19,20] and montmorillonite.[21,22]

PATHOLOGIC FEATURES

Three types of lesions are typically seen in individuals who are exposed to dusts containing a mixture of crystalline silica and silicates. These include macules, mixed-dust fibrotic lesions (MDF), and silicotic nodules.[23] Macules are nonpalpable lesions consisting of interstitial accumulations of dust-laden macrophages. These typically show a peribronchiolar or perivascular distribution and are associated with a delicate meshwork of reticulin fibers without obvious collagenization (Fig 1). MDF is a palpable, irregularly contoured, stellate-shaped lesion with varying degrees of collageniza-

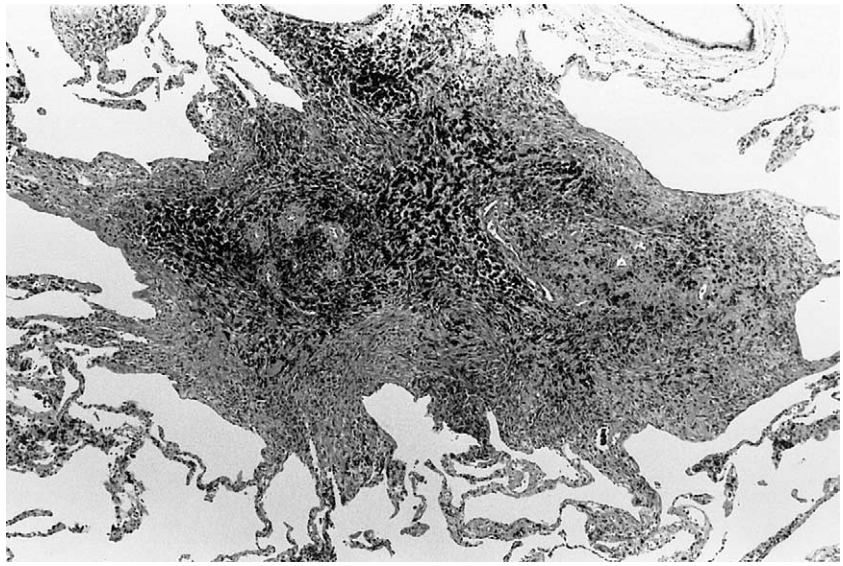

FIGURE 2. Histology of mixed-dust fibrosis, showing an irregular-contoured soft nodule composed of dust-laden macrophages and modest collagen fibrosis. Hematoxylin & eosin; original magnification, ×15.

tion (Fig 2). Macules and MDF have a tendency to spread diffusely into the adjacent lung tissue (diffuse interstitial fibrosis pattern, Fig 3).[24] Centrilobular emphysema may accompany macules and MDF, and in some cases, it may be a dominant pathologic feature even in the absence of a history of smoking. Silicotic nodules are well-delineated, firm, almost acellular fibrotic nodules composed of whorled hyalinized collagen (Fig 4). When viewing these various lesions by polarizing microscopy, numerous birefringent particulates are typically observed. Crystalline silica usually shows a weak birefringence in contrast to most silicates, which are intensely double refractile.[23] The presence of particles compatible with crystalline silica under polarized light helps to distinguish silicotic nodules from similar fibrous nodules of other etiologies. In any individual case, macules, MDF, and silicotic nodules may be observed to varying degrees and in various combinations. Progressive massive fibrosis or conglomerate lesions may be observed in some cases (Fig 5).

We define MDP pathologically as a combination of macules and MDF lesions, with or without silicotic nodules or massive fibrosis, in an individual with a history of exposure to mixed dust as defined above. If silicotic nodules are present, then MDF lesions should outnumber the silicotic nodules. If silicotic nodules predominate, the appropriate diagnosis is *silicosis*. Macular pneumoconiosis (MP), which is composed exclusively of macules, is arbitrarily included in MDP on the assumption that MP may represent an early stage of MDP. In the absence of a history of exposure, mineralogic analyses showing a mixture of crystalline silica and silicates would support the diagnosis. In the absence of either a history of exposure or mineralogic analysis, it is recommended that pathologists use the term *mixed-dust pneumoconiosis pattern*. The terms *anthracosilicosis* and

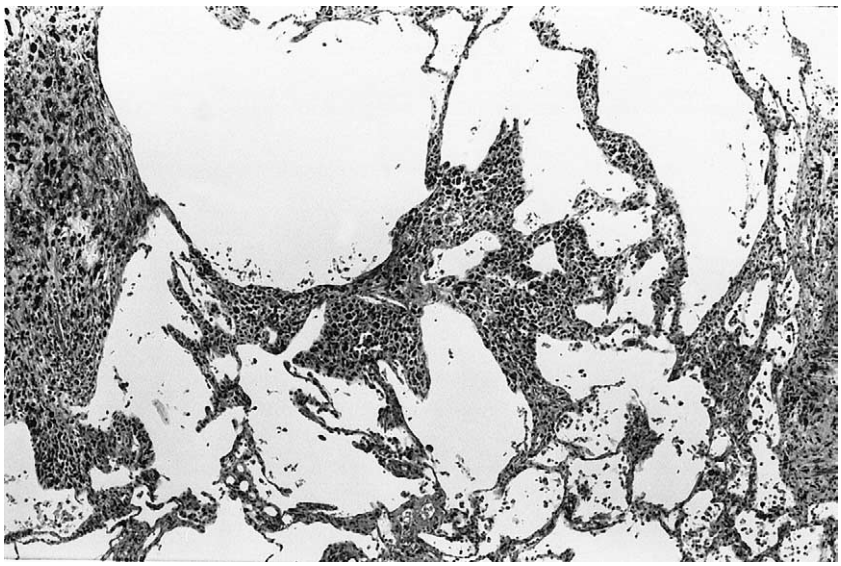

FIGURE 3. Diffuse interstitial fibrosis pattern of macules associated with emphysematous change. Hematoxylin & eosin; original magnification, ×15.

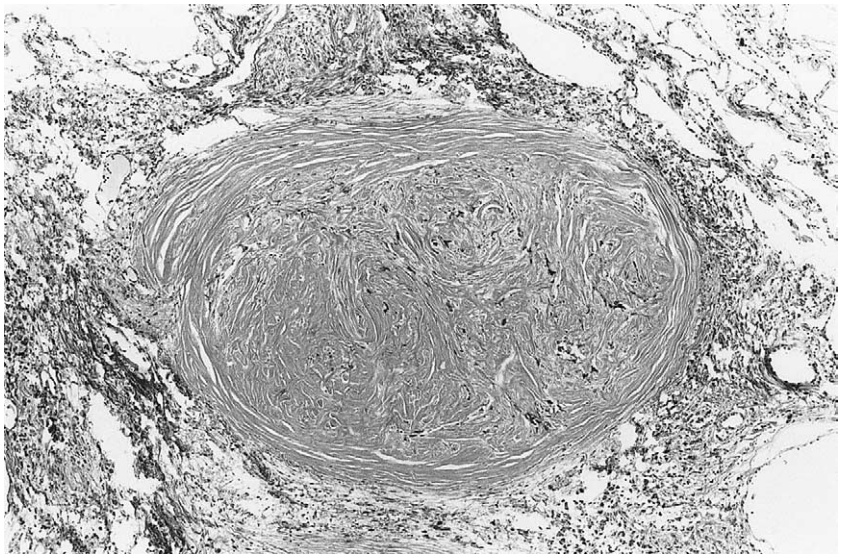

FIGURE 4. Histology of a typical silicotic nodule, showing a well-demarcated paucicellular rounded fibrous lesion composed of thick, hyalinized collagen fibers in a whorled pattern of arrangement. Hematoxylin & eosin; original magnification, ×20.

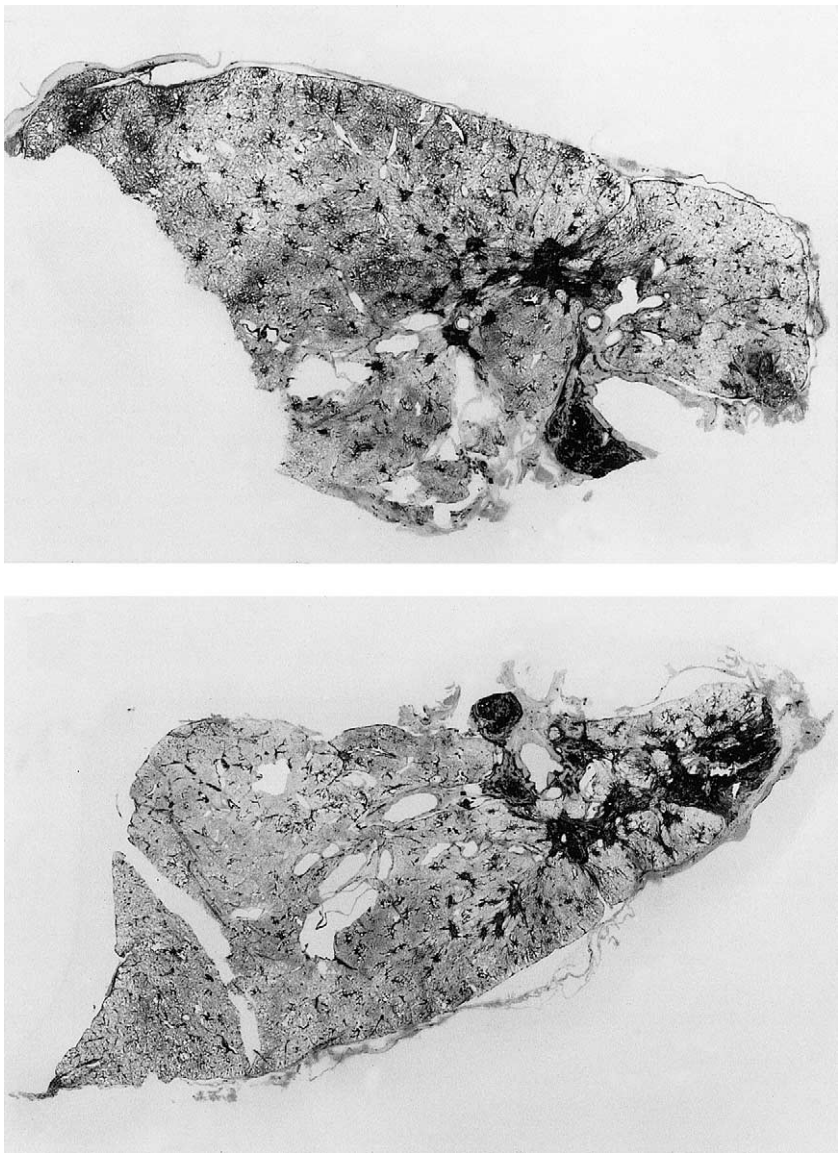

FIGURE 5. Paper-mount whole lung sections from a 76-year-old male patient who had been a brick worker for 31 years, showing mass lesions in the left upper and right middle lung areas due to coalescence of individual mixed-dust fibrotic lesions (MDF)–type fibrous nodules. Original magnification, ×0.15.

TABLE 1. Pneumoconioses to Be Excluded From Mixed-Dust Pneumoconiosis

Type	Ref. No.
Asbestosis	49,50
Berylliosis	51
Carborundum (silicon carbide) pneumoconiosis	52,53
Coal workers' pneumoconiosis	54,55
Corundum pneumoconiosis	5,56
Diatomaceous earth pneumoconiosis	57,58
Hematite miners' pneumoconiosis	6,59
Hard metal (lung) disease (tungsten carbide pneumoconiosis)	60-64
Silicate pneumoconiosis (silicatosis)	65,66
Fuller's earth	67-69
Kaolin	70-74
Mica	75,76
Talc	77-83
Silicosis (including silicoproteinosis)	23,84
Welders' pneumoconiosis	85-87

siderosilicosis also refer to a subset of MDP. Because of their equivocal clinicopathologic definitions, however, they should only be used with the greatest caution unless they are meant in the context of historical consideration.

MINERALOGIC ANALYSIS

Mineralogic analysis of tissue specimens may be performed in a number of different ways. One approach is the ashing of the tissue and analysis of recovered dust gravimetrically and by x-ray diffraction.[25,26] To obtain accurate identification of the mineral species, the x-ray diffraction analysis is required, employing the x-ray absorption correction.[27,28] Unfortunately, this approach requires a large sample of lung tissue. Another approach involves in situ analysis of tissue sections by analytical electron microscopy (scanning, transmission, or scanning transmission electron microscopy). A convenient and frequently employed technique is the examination of 5-μm-thick sections in a scanning electron microscope equipped with a backscattered electron detector and an energy dispersive spectrometer.[29,30] An advantage of this technique is that it can be performed on a section serial to the one used to make the pathologic diagnosis. Another detailed and rather complete technique is the examination of particles directly transferred to electron microscopic grids after ashing 5- to 20-μm-thick lung tissue sections.[31] This provides comprehensive data on particle shape, crystal structure, and chemical composition.[31,32] Electron-microscopic particle analysis can also be performed on particles isolated from lung tissue including transbronchial lung biopsy material,[33] bronchoalveolar lavage fluid, or even lymph nodes after ashing or digestion of the organic components.[34-36] These data contribute to defining the characteristics such as chemistry, crystallinity, size and concentration of the particles. A discussion of the advantages and disadvantages of each of these approaches is beyond the scope of this report but has been dealt with elsewhere.[37] Analysis typically shows the presence of silica, silicates, and various metal particles. These dust levels usually exceed by orders of magnitude the levels of such particles that are found in a background, unexposed population.[30]

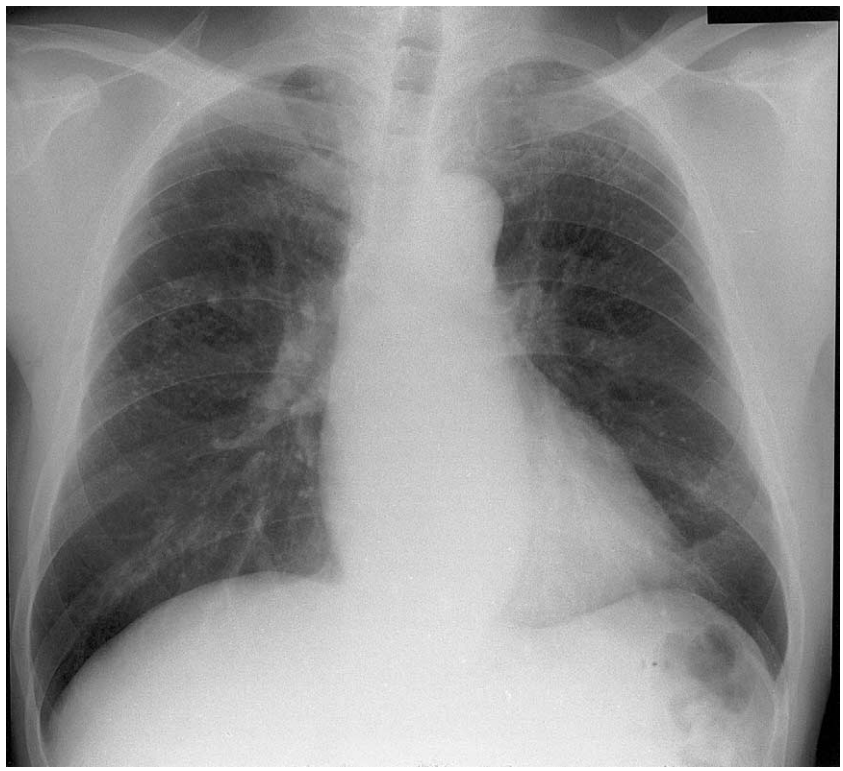

FIGURE 6. Chest radiograph of an 82-year-old male patient who had been working in a copper mine for 24 years, showing a small number of micronodules distributed in the bilateral upper and middle lung fields. Eggshell-type calcifications are noted in the tracheobronchial and supraclavicular lymph nodes.

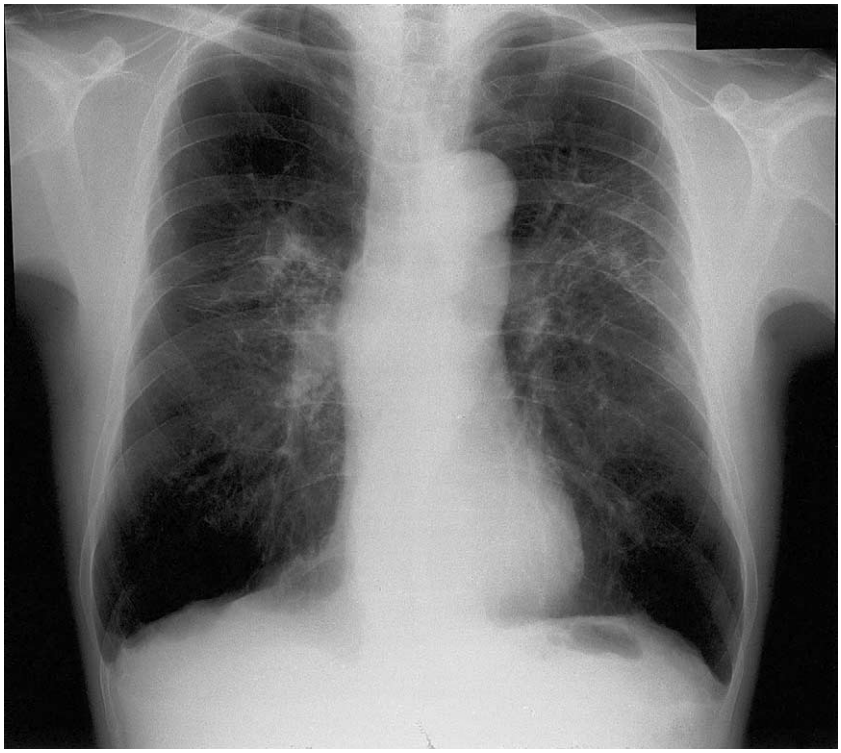

FIGURE 7. Chest radiograph of a 64-year-old male stonemason, demonstrating numerous irregular opacities mainly in the middle lung fields, obscuring the normal pulmonary vasculature. Apical and basal lung fields appear emphysematous. He was an ex-smoker with a smoking history of 20 pack-years.

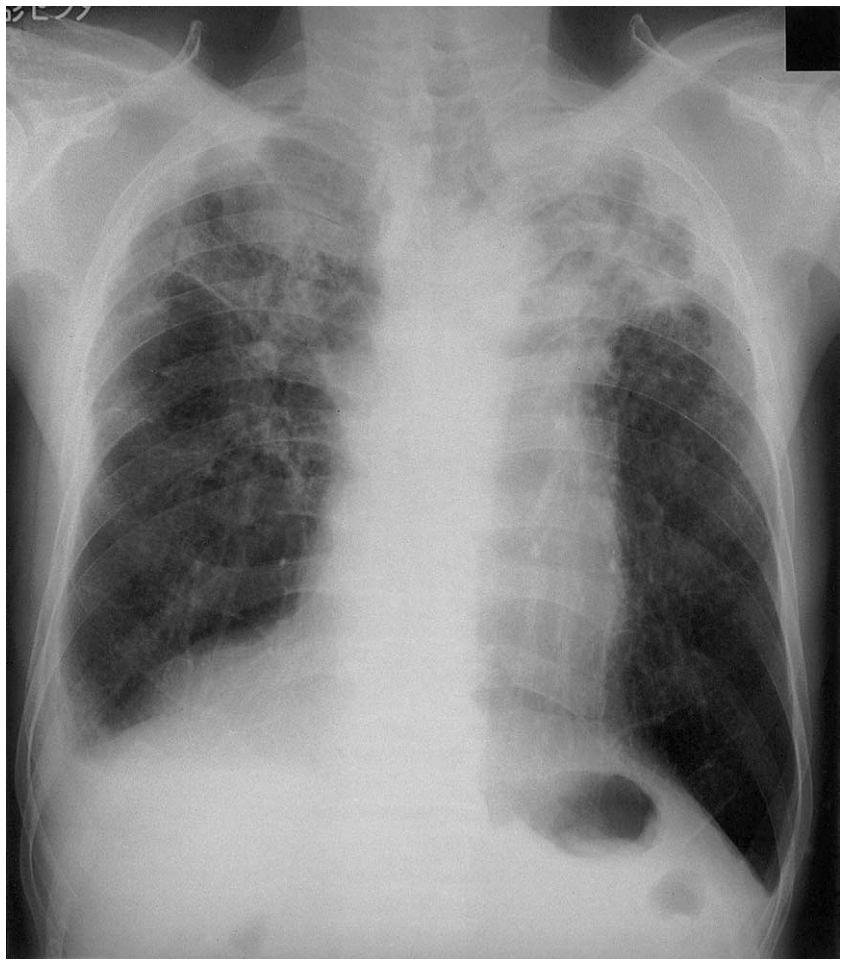

FIGURE 8. Chest radiograph of a 76-year-old brick worker (the same case as Fig 5), showing numerous small irregular opacities as well as left-side dominant, large irregular opacities in the upper lung fields, associated with extensive pleural thickenings. He was an ex-smoker with a smoking history of 40 pack-years.

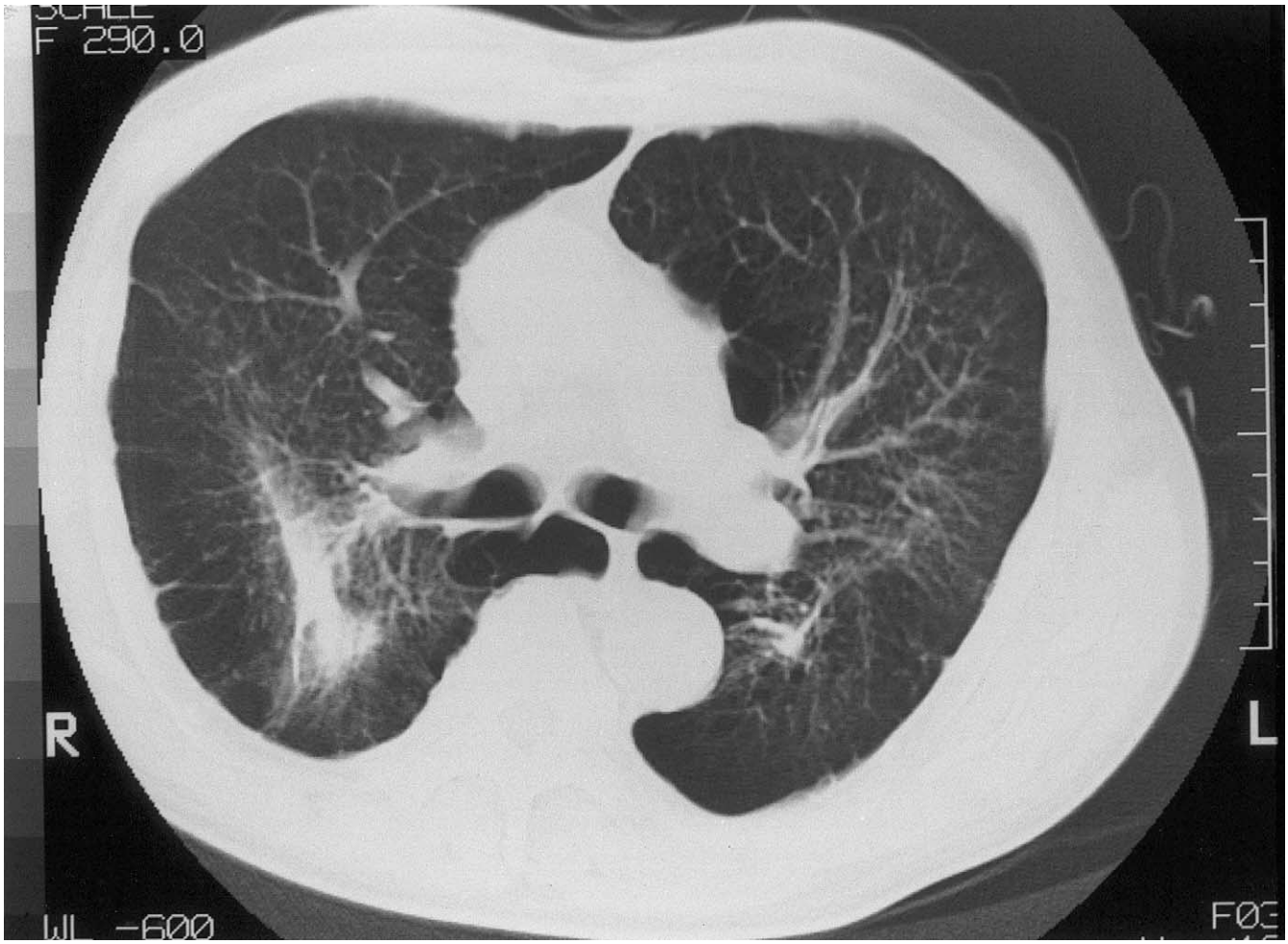

FIGURE 9. Conventional computed tomography of the patient seen in Fig 7 at the level of the aortic arch (window width, 1500HU; window level, −600 Hounsfield units), demonstrating disseminated irregular micronodules associated with centrilobular emphysema throughout the lungs. Posterior part of the left lung shows coalescence of the pulmonary vasculature due to shrinkage of the parenchyma. Peripheral portions of both lungs bear paraseptal emphysema with several interlobular septa.

CLINICAL DIAGNOSIS

The diagnosis is aided by a well-documented occupational history of concomitant exposure to mixed dust as defined above. Typical occupations associated with a diagnosis of MDP include metal miners, quarry workers, foundry workers, pottery and ceramics workers, and stonemasons. Lesions found in coal workers' pneumoconiosis and hematite miners' pneumoconiosis are very similar to those observed in MDP.[4] However, we are arbitrarily restricting the definition of MDP to exclude these and other well-defined clinicopathologic entities (Table 1). Radiologic findings (below) also help to differentiate these pneumoconioses and to distinguish classic silicosis. In exceptional cases, however, in which MDP is present together with another well-defined pneumoconiosis such as asbestosis, the diagnosis *mixed pneumoconiosis* or MDP with, for example, asbestosis might be made.

Radiologic findings of MDP on plain chest radiographs include a mixture of small rounded and irregular opacities as defined by the 1980 International Labour Office International Classification of Radiographs of Pneumoconioses. In some cases with pathologically proven macular pneumoconiosis, the chest radiograph may be within normal limits. If small rounded opacities predominate and siderosis[38] is excluded, the appropriate diagnosis is silicosis (Fig 6). Small rounded opacities seen in cases with MDP, if any, tend to have ill-defined contours. In cases in which irregular opacities predominate or are found exclusively, a diagnosis of MDP can be made with the appropriate occupational history (Fig 7).[39] Large opacities may or may not be present (Fig 8). Computed tomography scans of the thorax[40,41] show reticular, reticulolinear, or reticulonodular opacities in cases with MDP[42] (Fig 9) or may be normal in some cases with macular pneumoconiosis. Areas of emphysema are often seen. In the emphysematous lungs, ^{99m}Tc macroaggregated human serum albumin scintigrams clearly show a marked reduction of the pulmonary arterial perfusion.[39]

The symptoms of MDP are nonspecific. They include productive cough and dyspnea, which could be related to pneumoconiosis, smoking, or associated em-

physema. Pulmonary function tests can be normal or show an obstructive, restrictive, or mixed pattern. In general, pulmonary function tests tend to be less abnormal than in classic silicosis or asbestosis,[43,44] and the prognosis is better.

MDP must be distinguished from a variety of nonoccupational interstitial pulmonary disorders including usual interstitial pneumonia, eosinophilic granuloma, sarcoidosis, and respiratory bronchiolitis-associated interstitial lung disease.[45,46] The differential diagnosis, again, depends on a thorough knowledge of the patient's occupation and dust exposure. Mineralogic analysis of dust from the lungs or workplace can be used to support the diagnosis of MDP in patients with a combination of obscure or unconvincing exposure history, suggestive radiology, and pathologic demonstration of macules or nodular lesions in the lungs. Although uncomplicated MDP is typically a benign disease, cases with fatal extensive diffuse interstitial fibrosis causing honeycombing may be encountered. It should be noted that some patients with typical MDF lesions have superimposed diffuse interstitial fibrosis indistinguishable from UIP.[47] The pathogenesis of such cases is poorly understood, and an etiologic link between the 2 conditions has yet to be determined.[48]

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