Pathologic Findings in Severe Coal Workers' Pneumoconiosis in Contemporary US Coal Miners

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• ***Context.***—**The pathology of coal workers' pneumoconiosis (CWP) and its most severe form—progressive massive fibrosis (PMF)—in US coal miners has changed in recent years. Severe disease is occurring in younger miners and has been linked to an increase in silica dust exposure.**

Objective.—**To update the description of the pathologic features of CWP in contemporary miners compared to historical miners.**

Design.—**This study is a retrospective expert classification of lung tissue from 85 historical and contemporary coal miners with PMF. Significant pathologic features were scored by using a standardized instrument with consensus achieved for major findings, including newly defined categories of PMF as coal-type, mixed-type, and silica-type.**

Results.—**Pathologic features associated with silica dust exposure, including silica-type PMF, mineral dust alveolar proteinosis (MDAP), and immature (early stage) silicotic nodules, were increased in contemporary miners. Detailed descriptions of the pathology of contemporary CWP with illustrative figures are provided.**

Conclusions.—**Silica-related pathologies are more common in contemporary miners. Severe forms of CWP can be detected by subtyping PMF lesions (if present) or by identification of mature and immature silicotic nodules, coal mine dust–related alveolar proteinosis, and severe inflammation in coal miners' lungs. Silica-type PMF cases showed significantly higher levels of MDAP than either mixed- or coal-type PMF ($P < .001$). High profusion of birefringent silica/silicate particles was observed more frequently in cases with immature (early stage) silicotic nodules ($P = .04$). Severe inflammation was also significantly increased in contemporary miners ($P = .03$). Our findings underscore the urgent need to revise current exposure limits and monitoring of respirable crystalline silica in US coal mines.**

(*Arch Pathol Lab Med.* 2024;148:805–817; doi: 10.5858/arpa.2022-0491-OA)

Coal workers' pneumoconiosis (CWP) is an incurable disease that can only be prevented by strict dust controls. In the United States, enactment of a permissible exposure limit for respirable coal mine dust in 1970 was followed by a decline in cases of CWP during the subsequent 30 years.[1] This trend was reversed at the end of the 20th century, with resurgent disease including its most severe forms.[2] Disease "hot spots" have been identified in Central Appalachia, where large numbers of underground coal miners have been diagnosed with progressive massive fibrosis (PMF) as well as rapidly progressive pneumoconiosis (RPP). Antao et al[3] define RPP radiographically as an increase in the small opacity profusion by the equivalent of more than 1 International Labour Organization (ILO) subcategory during a 5-year period after 1985, and/or the development or progression of PMF after 1985. Our histopathologic study uses the latter definition. Coal miners with RPP are younger; more likely to have worked in smaller, narrow seam mines; and often worked at the coal face where they risk exposure to respirable dust from rock above and below coal seams.[3–7] In addition, changes in mining practices and technologies may also have contributed to higher airborne concentrations of silica and silicates.[8–10]

Emerging evidence indicates that exposure to respirable crystalline silica increases risk for severe CWP.[1,11] A 2016 case series of lung pathology in coal miners with RPP and complicated CWP showed unexpected findings of immature silicotic nodules, interstitial fibrosis, and areas of mineral dust–associated alveolar proteinosis (MDAP),[10] suggesting a shift from conventional pathologic findings of CWP.[12,13]

Accepted for publication August 10, 2023.

Published online October 18, 2023.

Supplemental digital content is available for this article at https://meridian.allenpress.com/aplm in the June 2024 table of contents.

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The lung pathology of pneumoconiosis in contemporary and historical coal miners was recently examined with advanced analytic techniques that helped document the role of silica and silicates in the pathogenesis of these changes.[14]

Substantial time has elapsed since the 1979 publication of anatomic criteria for the pathologic recognition of CWP.[12] The primary objective of this study was to provide an updated comprehensive description, along with illustrative figures, of the evolution in the pathologic features of severe CWP in recent decades compared to findings from a group of historical coal miners.

METHODS

Study Population and Samples

Cases of RPP and PMF were identified through outreach to the Black Lung Clinics Program (federally funded by the Federal Office of Rural Health Policy, an office of the Health Resources and Services Administration), radiologists, and other providers in areas with high rates of disease, as well as to attorneys and lay advocates representing miners who have filed for disability benefits. Miners were also invited to participate in this PMF case registry through recruitment at Black Lung conferences and other miners' events. Deceased miners with RPP or PMF were included in the registry if their next of kin consented to participation. Other cases were accessioned through the US National Institute for Occupational Safety and Health (NIOSH) National Coal Workers Autopsy Study (NCWAS).[15,16] Inclusion criteria required a confirmed diagnosis of PMF (defined below) by study pathologists, demographic and occupational histories for underground coal miners, and sufficient pathologic material for histologic evaluation (see Supplemental Table 1 for summary of demographic information in the supplemental digital content, containing 2 tables and 6 figures, at https://meridian.allenpress.com/aplm in the July 2024 table of contents).

Lung tissue from 85 underground coal miners with PMF met the inclusion criteria for the study. This population was divided into 2 groups: (1) miners born between 1910 and 1930 (historical miners, N = 62) and (2) miners born in or after 1930 (contemporary miners, N = 23). Historical miners worked mainly with conventional mining technology that relied on drilling and blasting, whereas contemporary miners spent a substantial portion of their mining tenure working with powerful mechanized equipment.

Archived lung tissue samples were available as formalin-fixed, paraffin-embedded, previously stained hematoxylin-eosin slides. These slides were reviewed, and the best-quality slide representing the most affected area was selected by study pathologists. The slides were digitized by using Aperio ScanScope XT (Software ImageScope version 8.2, Leica Biosystems, Buffalo Grove, Illinois) with ×40 magnification. The slides were also reviewed by using polarized light microscopy (PLM), and representative photomicrographs were obtained.

A subset of slides was chosen for verification of alveolar proteinosis, using periodic acid–Schiff with diastase (PAS-D) chemical stain. Images were given unique identifiers and made available to all participating pathologists, who were blinded to demographic and occupational details beyond the subjects' history of work as coal miners.

Pathology Scoring and Features

Seven experienced occupational pulmonary pathologists—2 groups of 2 pathologists each and 3 individual pathologists—visually assessed and scored for relevant histologic features on all cases, using a standardized classification scheme (available on request).

Study data were collected and managed with REDCap electronic data capture tools hosted at the University of Illinois Chicago.[17,18] Discordant findings of major pathologic features from all study cases were reviewed and discussed by all participating pathologists using videoconference to achieve consensus classifications. These meetings were also used to select representative images for inclusion in this article. The definitions and examples of minor pathologic features were reviewed by consensus for the first 20 cases; for the remainder of cases the median classification was used for analysis.

We characterized the broad spectrum of pathologic findings of CWP, including the "classic" lesions of CWP, as described by Kleinerman et al[12] in 1979, as well as features described in a recent pathologic study of rapidly progressive CWP.[10] Specifically, we evaluated specimens for major features including PMF type, coal dust macules, coal dust nodules, mature and immature (early stage) silicotic nodules, and MDAP. Other features such as interstitial fibrosis, mineral dust small airways disease (MDSAD), emphysema, and interstitial inflammation were characterized as present/absent and, if possible, graded semiquantitatively. All types of emphysema are associated with coal mine dust exposure, with centriacinar and paracicatricial types predominating.[19] However, grading was subjective, and, in view of the small sample of non-PMF parenchyma, not suitable for further analysis. Previously, a substantial level of agreement ($\kappa = 0.62$) on type of PMF was demonstrated between study pathologists in a larger sample of NCWAS cases.[20]

Definitions of the Major Pathologic Features

Progressive Massive Fibrosis.—The PMF lesion of coal miners is represented by a mineral dust–laden fibrotic lesion(s) with dense deposition of collagen fibers, with or without areas of necrosis, measuring more than 10 mm in long-axis diameter. This definition was used because of its equivalency with the ILO radiologic criterion for a large pneumoconiotic opacity[21] and with current US legal definitions.[22] We also considered specimens as consistent with PMF that had lesions measuring nearly 10 mm along the long axis, but were truncated on the slide with the cut tissue edge intersecting the long axis. Although technically insufficient for PMF, when viewed by an expert pathologist, a truncated lesion that measures nearly 10 mm along its long axis undoubtedly qualifies as a PMF lesion. If available, correlation with imaging studies is helpful for size confirmation.

We developed a subclassification of PMF lesions to provide better insight into the pathogenesis of these lesions: (1) silica-type, composed of more than 75% silicotic nodules; (2) mixed-type, more than 25% and up to 75% silicotic nodules; and (3) coal-type, up to 25% silicotic nodules. Other features associated with PMF lesions, such as granulomas, necrosis, and MDAP, were also noted. Examples of PMF subtypes are shown in Figure 1, A through F (see supplemental digital content for detailed discussion of PMF measurements).

Although our study design required all cases to contain PMF lesions, we also assessed other types of CWP lesions in non-PMF lung parenchyma. It should be noted that the amount of non-PMF lung parenchyma varied, with the result that some cases contained no evaluable lung tissue outside of the PMF lesion.

Macular Lesions of CWP.—Coal macules are lesions containing coal mine dust–laden macrophages that are located within the walls of respiratory bronchioles, with fine reticulin and minimal collagen that is haphazardly arranged. Lesions usually have a long-axis diameter of 1 to 6 mm. Coal macules are strongly associated with centriacinar emphysema (Figure 2, A through D). Centriacinar emphysema associated with coal dust exposure was previously termed *focal emphysema*. "Focal" emphysema is not a distinct type of emphysema, and its use should be discouraged. Emphysema in coal miners is not inconsequential, as their degree of emphysema exceeds that seen in nonminers with similar smoking histories and can occur in the absence of smoking.[23,24] Coal macules graded as mild in severity show occasional macules occupying up to 10% of the lung parenchyma; macules graded as moderate involve more than 10% and up to 60% of the lung parenchyma; and macules graded in the severe category occupy more than 60% of the lung parenchyma (Supplemental Figure 1, A through D, illustrates the transition of macules to nodules to PMF).

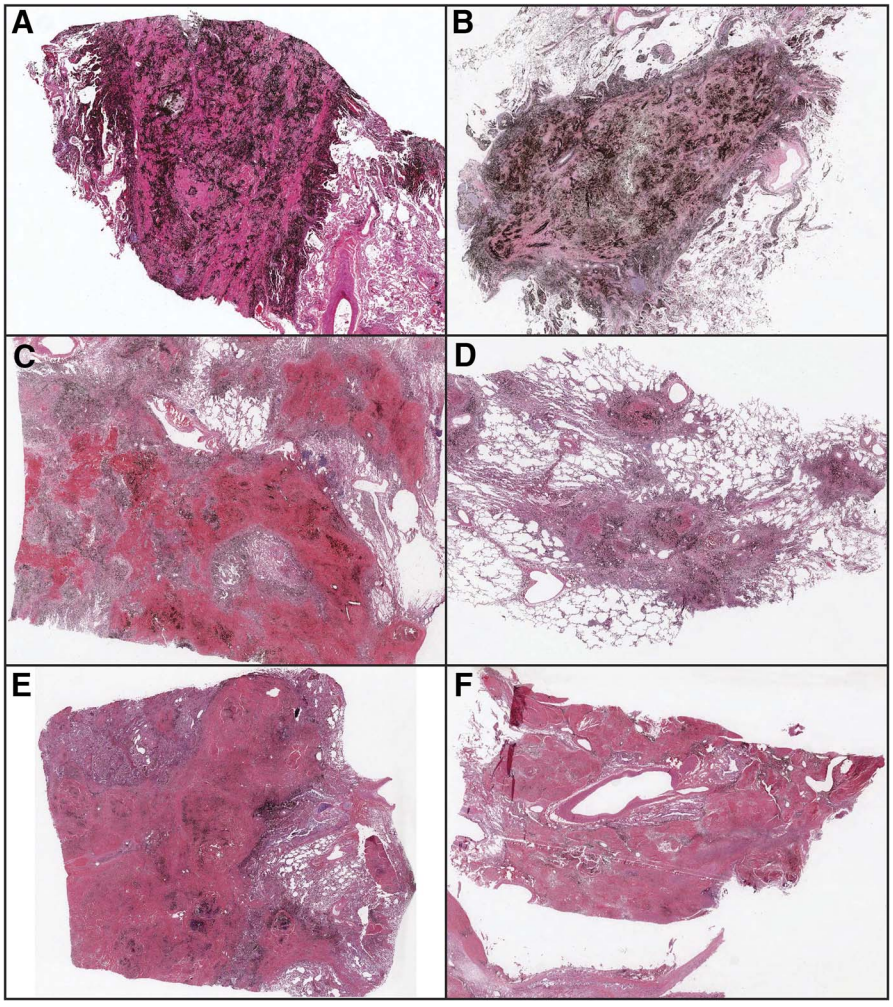

Figure 1. *Panel of progressive massive fibrosis (PMF) types (coal-type, mixed-type, and silica-type). A and B, Coal-type PMF. A, This classic coal-type PMF lesion is characterized by an irregular coal dust–pigmented fibrotic lesion. Although this lesion measured a little more than 8 mm along its long axis, both edges are truncated and thus it is apparent the lesion is greater than this and qualifies as PMF (for discussion of the size definition and measurement of a PMF lesion see supplemental digital material). B, Another example of coal-type PMF, measuring 14 mm on its long axis, with dense coal deposits. Importantly, none of these classic coal-type PMF lesions show more than 25% silicotic nodules as a component. C and D, Mixed-type PMF. C, An example of a mixed lesion measuring 25.5 mm on its long axis, with approximately 50% of the lesion composed of silicotic nodules. The remainder of the lesion consists of coal deposits with associated irregular fibrosis. D, A mixed-type PMF lesion, measuring 13 mm on its long axis, with approximately half consisting of rounded silicotic nodules. The surrounding parenchyma shows 3 nodules, 2 of which are silicotic (top and left) and 1 of which is coal dust–type (top right). E and F, Silica-type PMF. E, A densely collagenized lesion measuring 11.5 mm on its long axis, composed of coalescing silicotic nodules. There is minimal black coal dust pigment. Multiple mature and immature silicotic nodules are seen in the surrounding lung parenchyma. F, Large silica-type PMF lesion, measuring 21.5 mm on its long axis, and consisting of multiple rounded silicotic nodules that have coalesced into a lesion that is impinging on a large blood vessel (hematoxylin-eosin, original magnifications ×4 [A, C, and F], ×5 [B], and ×6 [D and E]).*

Nodular Lesions of CWP.—Study pathologists classified and achieved consensus on 3 major types of nodular lesions in CWP: coal dust nodules, immature silicotic nodules, and mature silicotic nodules.

Coal dust nodules are coal mine dust–laden fibrotic lesions up to 10 mm in long-axis diameter with round or irregular borders and with an irregular distribution of mild to moderate amounts of collagen fibers. Coal dust nodules are histologically similar to mixed-dust nodules, as coal dust is a mixed dust. However, if there is a predominance of pigmented coal mine dust, then the lesion should be called a *coal dust nodule*. Like coal macules, grading of coal dust nodules was ranked as (1) mild (a single nodule or occasional nodules occupying ≤5% of the lung parenchyma); (2) moderate (occupying >5% to ≤20% of the lung parenchyma); or (3) severe (occupying >20% of the lung parenchyma), as previously described.[1] Figures 3, A through D, and Figure 4, A through D, illustrate the varying appearances of nodules in coal- and mixed-type PMF cases.

Immature or early-stage silicotic nodules are cellular with exuberant fibrohistiocytic (sometimes lymphoplasmacytic/histiocytic) infiltrates and poorly organized central collagen deposition. Mature silicotic nodules are less cellular and characterized by predominantly centrally placed mineral dust surrounded by concentric laminated mature collagen fibers measuring up to 10 mm in long-axis diameter with circumscribed (rounded or irregular) borders. Mature silicotic nodules may also demonstrate a surrounding cellular area of dust-laden histiocytes. Silicotic nodules were graded for severity ranging from mild (≤5% of lung parenchyma), to moderate (>5% and ≤20% of lung parenchyma), to severe (>20% of lung parenchyma), using previously published criteria.[1] Figure 5, A through D, shows examples of immature silicotic nodules. Figure 6, A through D, shows examples of mature silicotic nodules (Supplemental Figure 2, A through C, illustrates the progression from immature to mature silicotic nodule).

Other Silica-Related Pathologic Features.—Based on prior work, histologic features often seen in RPP include 3 silica-related pathologic features[9,10]: (1) mature silicotic nodules (described above); (2) immature (early stage) silicotic nodules (described above); and (3) MDAP. MDAP was characterized by focal collections of lipoproteinaceous material within alveolar spaces in or adjacent to PMF and/or nodular CWP lesions. Occasionally the proteinaceous airspace accumulations were more extensive and involved contiguous alveoli. The intra-alveolar material was slightly granular and showed characteristic artifactual cracks from shrinkage and/or empty cholesterol clefts. Confirmation of MDAP was reflected by PAS-D positivity. Pathologists graded the MDAP as absent, mild, or substantial by qualitative visual inspection (Figure 7, A and B).

We also explored the relationship between the profusion of birefringent particles evaluated by using PLM and silica-related pathologic changes. The profusion of birefringent particles was semiquantitatively assessed in the most densely affected areas of the PMF lesion. If more than 1 area was evaluated and photographed under PLM, the area with the highest profusion in a single high-power field (HPF) was selected and assessed as mild (≤10% of the HPF field), moderate (>10% to ≤25% of the HPF field), or severe (>25% of the HPF field). The major types of birefringent particles in coal workers' lungs include weakly birefringent silica, strongly birefringent aluminum silicates, and elongated fragments of fibers and platy particles. Figure 8, A through D, shows examples of varying grades of birefringent silica, silicate, and fibrous/

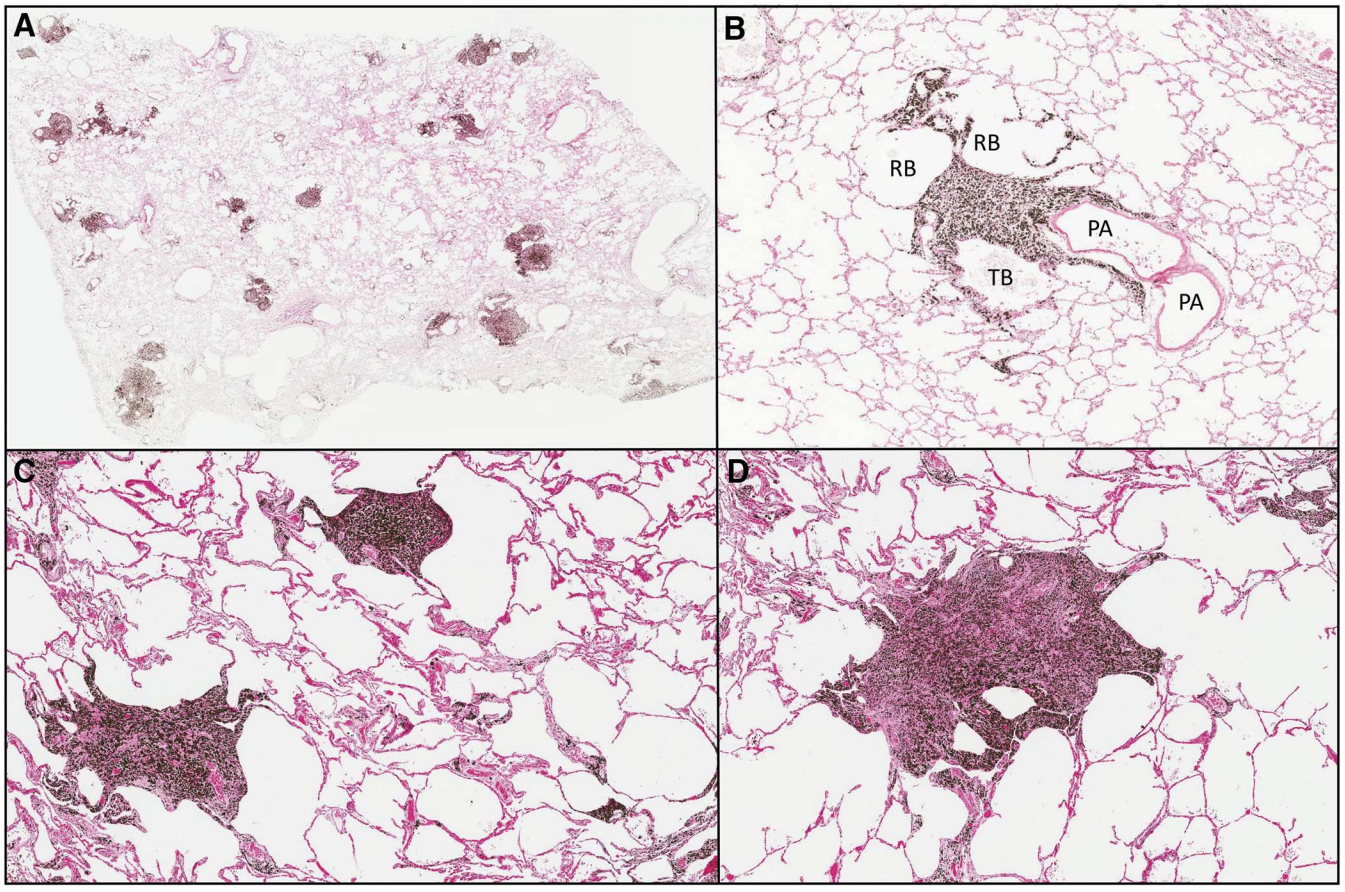

Figure 2. *Coal dust macules with early transition to coal nodule. A, Low-magnification view of coal dust macules showing their distribution in the walls of respiratory bronchioles at the centers of acini. B, Higher power illustrating a single macule consisting of coal-dust–laden macrophages within the walls of the first generations of respiratory bronchioles (RBs). The macule is located at the junction of a terminal bronchiole (TB) and attendant pulmonary arteriole (PA). The macule shows mild reticulin fibrosis but minimal collagen. Note the rim of centrilobular emphysema at the periphery of the macule. The surrounding parenchyma appears normal. C, Two coal dust macules with surrounding centrilobular emphysema. The macule at top center has very little collagen; the one at lower left shows more collagen. D, Coal dust macule transitioning into a coal dust nodule. The lesion is larger than the other macules and has more collagen and likely would be palpable to touch. In view of the increased collagen in this lesion, the surrounding emphysema could be described as paracicatricial (hematoxylin-eosin, original magnifications ×5 [A], ×20 [B and C], and ×40 [D]).*

elongated (defined as aspect ratio 3:1) particles. For optimum viewing, the light source must be bright enough to identify the weakly birefringent particles. A good in/ternal control is collagen, which is weakly to moderately birefringent.

Definitions of Other Pathologic Features

Dust-Related Diffuse Fibrosis.—Several types of interstitial fibrosis are recognized in coal workers.[25] These include usual interstitial pneumonia (UIP)–like fibrosis, bridging fibrosis between nodules, diffuse fibrosis, and peribronchiolar interstitial fibrosis. Varying degrees of dust particle accumulation can be seen in association with the fibrosis. In our study cases, if adequate non-PMF parenchyma was available for evaluation, the grade and type of interstitial fibrosis (bridging, respiratory bronchiolitis–interstitial lung disease [RB-ILD]–like, UIP-like, and diffuse not otherwise specified) was recorded. The grading system for extent of interstitial fibrosis was modified from that developed by Craighead et al[26] for asbestosis. Because the amount of surrounding non-PMF parenchyma was limited in many of the cases, our grading for this feature has limited value. However, previous radiology- and pathology-based studies of RPP[3,10] have shown that interstitial fibrosis can be a major feature of RPP (see Supplemental Figure 3, A and B, for examples of dust-related diffuse fibrosis [DDF]).

Inflammation.—Inflammation was graded as absent (≤5% of interstitium), mild (>5% to ≤25% of interstitium), or substantial (>25% of interstitium). Inflammation was assessed at the periphery of or adjacent to PMF lesions. The type of inflammation was further subcategorized into predominant cell type: lymphoplasmacytic, fibrohistiocytic, granulomatous, eosinophilic, and lymphoid aggregates (with or without germinal center formation) (Supplemental Figure 4, A through D, illustrates the forms of inflammation associated with PMF lesions in this study).

Statistical Analysis

We used SAS (version 9.4, SAS Institute, Cary, North Carolina) for all analyses. Categorical variables were compared between historical and contemporary groups by using the Fisher exact test. Continuous variables were examined across historical and contemporary status as well as by PMF type, using *t* tests with pooled or Satterthwaite results as appropriate. ANOVA (analysis of variance) Tukey pairwise comparison was used to compare mean differences in continuous variables across multiple groups. The Levene test was used to assess homoscedasticity; in cases of unequal distribution, we used the Welch test for ANOVA testing. A P value $<.05$ was considered significant.

RESULTS

We analyzed lung tissue slides from 85 coal miners, including 62 miners born between 1910 and 1930 (historical) and 23 miners born in or after 1930 (contemporary). In

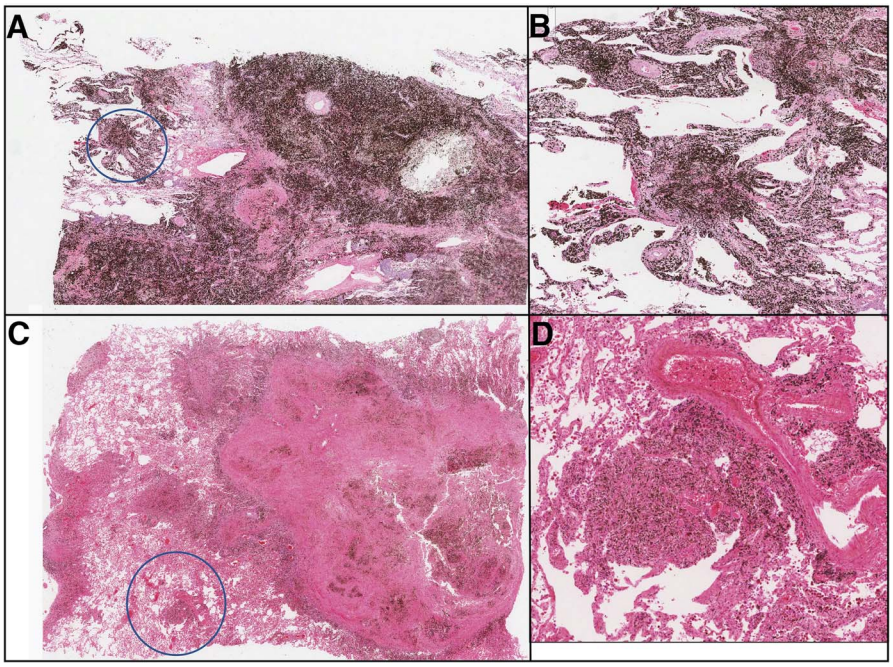

Figure 3. *Coal nodules with progressive massive fibrosis (PMF) and interstitial fibrosis. A, Coal-type PMF with coal nodules in the non-PMF lung parenchyma. Blue circle highlights a coal nodule, which is viewed at higher magnification in (B). B, Higher power illustrating an irregular coal-dust–laden fibrotic lesion that measures less than 10 mm along the long axis. These lesions would likely be palpable because they contain more collagen and are consequently more fibrotic than coal macules, which are typically nonpalpable lesions. Note the dust-related interstitial bridging fibrosis between the coal dust nodule and the PMF lesion. There is also severe paracicatricial emphysema. C, Mixed-type PMF with several immature silicotic nodules and 1 coal dust nodule (blue circle) noted in the surrounding parenchyma. D, Higher power of the coal dust nodule circled in Figure 4, C, showing the irregular distribution of collagen fibers (hematoxylin-eosin, original magnifications ×5 [A and C], ×30 [B], and ×50 [D]).*

nearly all cases (84 of 85; 99%), the slides were classified as good to high quality, without significant technical defects, with only 1 case showing areas of parenchyma slightly out of focus. Twenty-eight cases lacked sufficient non-PMF parenchyma for evaluation, limiting our assessment of non-PMF features except for inflammation and MDAP in and around the PMF lesion. Four cases showed truncated lesions, which measured nearly 10 mm along the long axis and were deemed sufficient for PMF by all 7 study pathologists.

Case demographic information was previously reported (Supplemental Table 1).[14] Briefly, contemporary miners were significantly younger than historical miners at time of tissue acquisition and worked fewer years as underground coal miners. There were no significant differences between groups in years worked at the surface, smoking status, pack-years of smoking, race, and whether the miner worked mainly in Central Appalachia. There was a nonsignificant trend of historical miners having worked more years in coal mining. Contemporary miners were significantly ($P = .002$) more likely to have silica-type PMF (13 of 23; 57%) than mixed-type (6 of 23; 26%) or coal-type (4 of 23; 17%) PMF. Conversely, historical miners were significantly ($P = .002$) more likely to demonstrate coal-type PMF (31 of 62; 50%) than mixed-type (20 of 62; 32%) or silica-type (11 of 62; 18%) PMF (see Supplemental Table 2). Also, as previously reported,[14] immature and mature silicotic nodules were more commonly found in contemporary miners and were more likely to be absent in historical miners, although differences were not statistically significant.

We also compared the severity of MDAP to PMF type. Silica-type PMF cases more often showed mild or substantial MDAP (18 of 24; 75%) than either coal-type PMF (8 of 35; 23%) or mixed-type PMF (11 of 26; 42%), with $P < .001$. Not surprisingly, 7 of 8 cases having substantial MDAP were classified as silica-type PMF.

Unusual variants of PMF were also identified, including pleural fibrosis that merged with the parenchymal fibrotic lesion, a "rounded atelectasis"–type, and a PMF lesion contiguous with a large area of fibroelastosis (see Supplemental Figure 5, A through D, for illustrations of unusual variants).

The association of silica-related pathology findings with the profusion of birefringent particles was also evaluated. High profusion (moderate/severe) of birefringent particles was observed significantly more frequently in cases where immature/early-stage silicotic nodules were present (7 of 18 [39%] versus 8 of 61 [13%], $P = .04$) (Table 1). We also observed that moderate to severe profusion of birefringent particles was observed more frequently in cases where mature silicotic nodules (8 of 30 [27%] versus 7 of 49 [14%], $P = .17$) and MDAP (11 of 38 [29%] versus 7 of 47 [15%], $P = .12$) were present, but this was not statistically significant. There was no significant association between high profusion of birefringent particles and coal-related pathologic findings. Cases with high profusion of birefringent particles were more common in silica- and mixed-type PMF cases than in coal-type PMF (7 of 24 [29%], 7 of 26 [27%], and 4 of 35 [11%], respectively), although this did not reach statistical significance ($P = .18$) (Table 1).

We compared the prevalence of severe inflammation, interstitial fibrosis, lymphoplasmacytosis, fibrohistiocytosis, and lymphoid aggregates (with and without germinal center formation) and high profusion (moderate/severe) of birefringence particles in historical versus contemporary cases. Significantly more contemporary than historical miners demonstrated severe inflammation (6 of 18 [33%] versus 6 of 60 [10%], $P = .03$). Though not statistically significant, contemporary miners were found to have a greater prevalence of interstitial fibrosis, lymphoplasmacytosis, and fibrohistiocytosis. There was essentially no difference between historical and contemporary miners when comparing lymphoid aggregates. There was a trend toward contemporary miners having a high profusion of birefringent particles when compared to historical miners, but this was not statistically significant (Table 2).

Some of the features we planned to score were not evaluable owing to insufficient non-PMF tissue, including

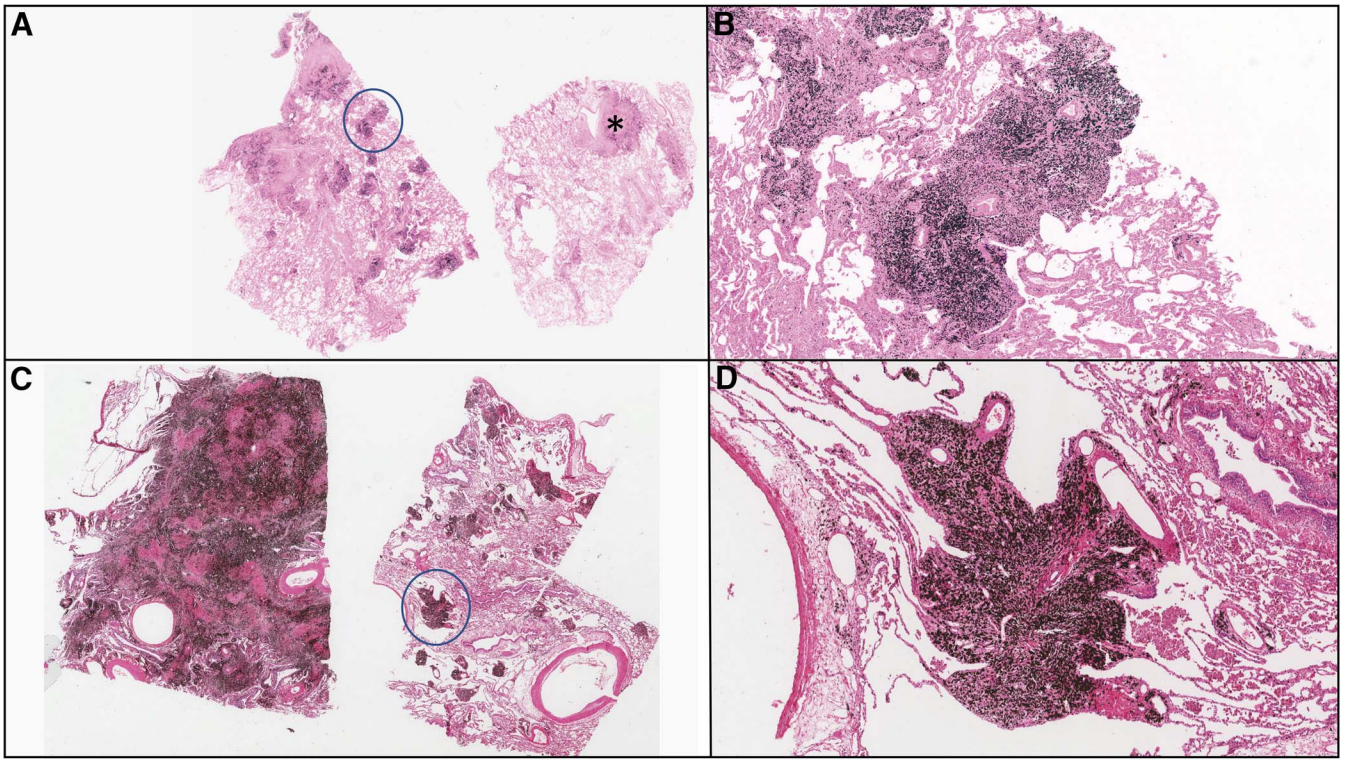

Figure 4. *Coal nodules in miners with progressive massive fibrosis (PMF). A, Lung parenchyma from miner with PMF showing a mixture of macules and coal nodules in the lung parenchyma. A single silicotic nodule is visible at low power (*). The blue circle highlights a coal nodule, which is viewed at higher magnification in (B). B, Higher power of the coal nodule circled in (A). There is dense, randomly oriented collagen admixed with the coal dust particles, consistent with a coal nodule. C, Mixed-type PMF lesion (left) consisting of both fused silicotic and coal mine dust nodules with large quantities of coal and mineral dust deposits. The adjacent section to the right shows moderate severity of coal dust nodules and rare macules. A coal nodule is highlighted by the blue circle and viewed at higher magnification in (D.) D, At high power the coal nodule shows irregular borders, dense coal deposits, and haphazardly arranged collagen fibers (hematoxylin-eosin, original magnifications ×4 [A], ×40 [B and D], ×5 [C]).*

MDSAD (see Supplemental Figure 6) and emphysema. Other features noted during the consensus meetings included 6 cases with granulomas, 5 of which showed necrosis. No tissue blocks were available for special stains to rule out concurrent infections. Five cases showed tumor consisting of invasive adenocarcinoma. No other tumor types were identified.

DISCUSSION

Summary of Major Findings

PMF Subtypes.—Our data confirm that contemporary severe or rapidly progressive CWP is an evolving disease from that seen historically in coal miners. Furthermore, we show that this more severe form of modern CWP can be distinguished from historical disease with a simple classification scheme based on the percentage of silicotic nodules within the PMF lesion: (1) silica-type PMF, (2) mixed-type PMF, and (3) classic coal-type PMF. Recognition of these PMF subtypes is important for understanding the relevant exposures and has implications for the likelihood of disease progression and premature death. Here, we confirm that silica-type PMF lesions are significantly more prevalent in contemporary miners, while coal-type PMF lesions are significantly more common in historical miners. We also show that other silica-related pathologies, including immature silicotic nodules and MDAP, are more common in contemporary coal miners with severe disease than in historical coal miners. Our findings are in keeping with a prior study examining the composition of minerals in the lungs of this coal miner population. Scanning electron microscopy and x-ray spectroscopy showed that silica particles were significantly more common in the lungs of miners with silica-type PMF, and also in miners with immature silicotic nodules and MDAP.[14] Classifying PMF type based on contribution of silica dust has important ramifications for understanding the pathologic lung changes that have occurred over time in coal miners and for understanding why contemporary cases may lack the classic "heavily pigmented" features described in earlier studies.[12] Importantly, silica-type PMF may progress more rapidly, resulting in more severe disease. Such severe cases may require referral to transplant programs.[27–30]

Features Associated With Severe CWP in Contemporary Miners.—Our study demonstrates a number of specific features associated with severe cases of CWP in contemporary coal miners. Commonly found were silica-type PMF, MDAP, high profusion of birefringent particles, silicotic nodules (both mature and immature), relative paucity of coal macules and nodules, and more severe chronic inflammation and interstitial fibrosis.

Alveolar proteinosis related to mineral dust exposure—MDAP—can be difficult to recognize but is typically found around and sometimes within PMF lesions. Histologic features of MDAP as well as alveolar proteinosis in general include cholesterol clefts, cracks, and PAS-D (or PAS)

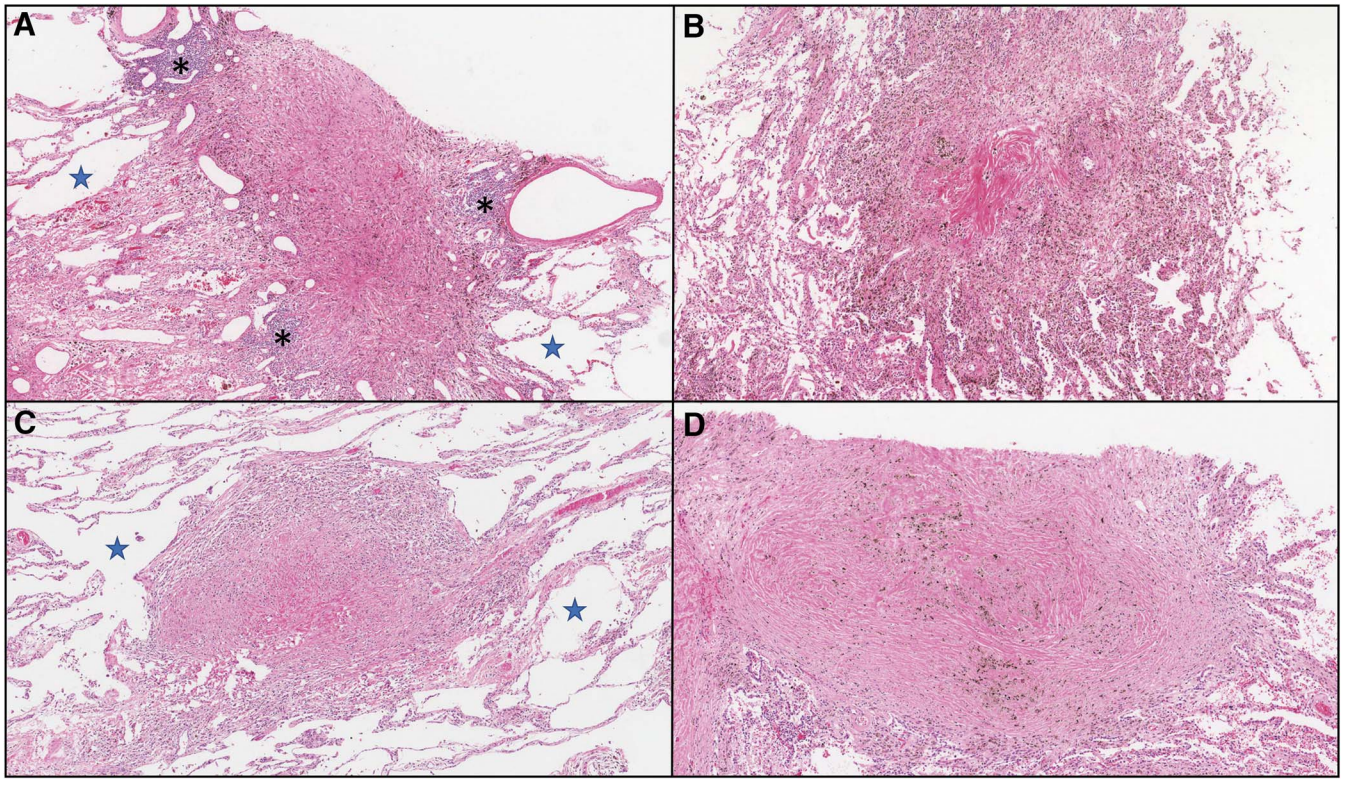

Figure 5. *Immature (early stage) silicotic nodules. A, Silica-type progressive massive fibrosis (PMF) case. This image illustrates the nodular interstitial infiltrate composed of fibrohistiocytic cells and poorly organized central collagen. The adjacent lung parenchyma shows interstitial bridging fibrosis, lymphoid aggregates (asterisks), as well as paracicatricial emphysema (starred spaces). B, Mixed-type PMF case with an immature silicotic nodule in the non-PMF lung parenchyma. This lesion shows early development of the central dense whorled collagen inherent in classic silicotic nodules. This lesion is slightly more irregular in shape than typical mature silicotic nodules. C, A silica-type PMF case with an immature, cellular silicotic nodule in the adjacent parenchyma. This lesion is rounded and nodular, but lacks the whorled central collagen found in mature silicotic nodules. It also shows a greater inflammatory infiltrate than that seen around a mature silicotic nodule. The surrounding alveolar spaces are enlarged by paracicatricial emphysema (starred spaces). D, A silica-type PMF case showing an immature silicotic nodule in the adjacent parenchyma. This lesion shows early formation of the dense whorled and laminated parallel collagen fibers in the center of the nodule, typical of the mature silicotic nodule (hematoxylin-eosin, original magnifications ×40 [A and B] and ×50 [C and D]).*

positivity, the latter helpful for confirmation of the diagnosis and extent of MDAP. While alveolar proteinosis is not a feature in older descriptions of PMF related to CWP,[12] Honma and Chiyotani[31] reported in 1991 that 73% of patients with silicosis and PMF had this finding. Workers in their study were identified as miners, tunnelers, stonemasons, or other, but no mention was made of coal miners. These findings are similar to our contemporary coal miners with PMF.

The literature is replete with descriptions of acute silicoproteinosis occurring in association with massive exposure to fine particulate respirable silica, usually within 3 to 5 years.[32–34] Acute silicoproteinosis is typically described in sandblasters, stonecutters, abrasive industry workers, metal/nonmetal miners, and, more recently, artificial stone workers.[35–38] The presence of MDAP in coal miners, often after decades of exposure and unrelated to any prior clinical diagnosis of silicoproteinosis, suggests that MDAP is indicative of respirable crystalline silica exposure. Other dust exposures, including aluminum, indium, titanium, and tin, may also lead to MDAP.[39–42]

Our study and studies of other occupational groups link the presence of MDAP to the more rapidly progressive form of fibrosis in coal miners.[10,28,29] However, the mechanism of MDAP development in PMF cases is unknown. Its distribution adjacent to PMF and nodular lesions indicates a chronic condition resulting from repeated episodes of acute silica-induced injury. Given that autoimmune alveolar proteinosis (with anti–granulocyte-macrophage colony-stimulating factor [GM-CSF] antibodies) is the most frequent form of nonoccupational alveolar proteinosis,[43] an immune response to the PMF lesion may contribute to the development of MDAP in these coal miners.

Previous work suggests that the presence of silicotic features in coal miners correlates with rapidly progressive disease and that these features are more prevalent in contemporary miners.[10,14] This study confirms that immature and mature silicotic nodules are more prevalent in contemporary PMF cases and further shows that silicotic nodules are associated with a high profusion of birefringent mineral dust particles, identified under PLM. A high profusion of birefringent particles was also significantly correlated with the presence of MDAP in coal workers with PMF. The increased prevalence of silicotic lesions in coal miners with rapidly progressive disease and in contemporary coal miners with PMF underscores the importance of assessing lung tissue samples for birefringent particles using PLM.

Although not surprising, most historical (>90%) and contemporary (~75%) PMF lungs from coal miners in our study contained classic coal macules and/or nodules. More surprising is that a quarter of contemporary coal miners had neither coal macules nor coal nodules in their examined tissue

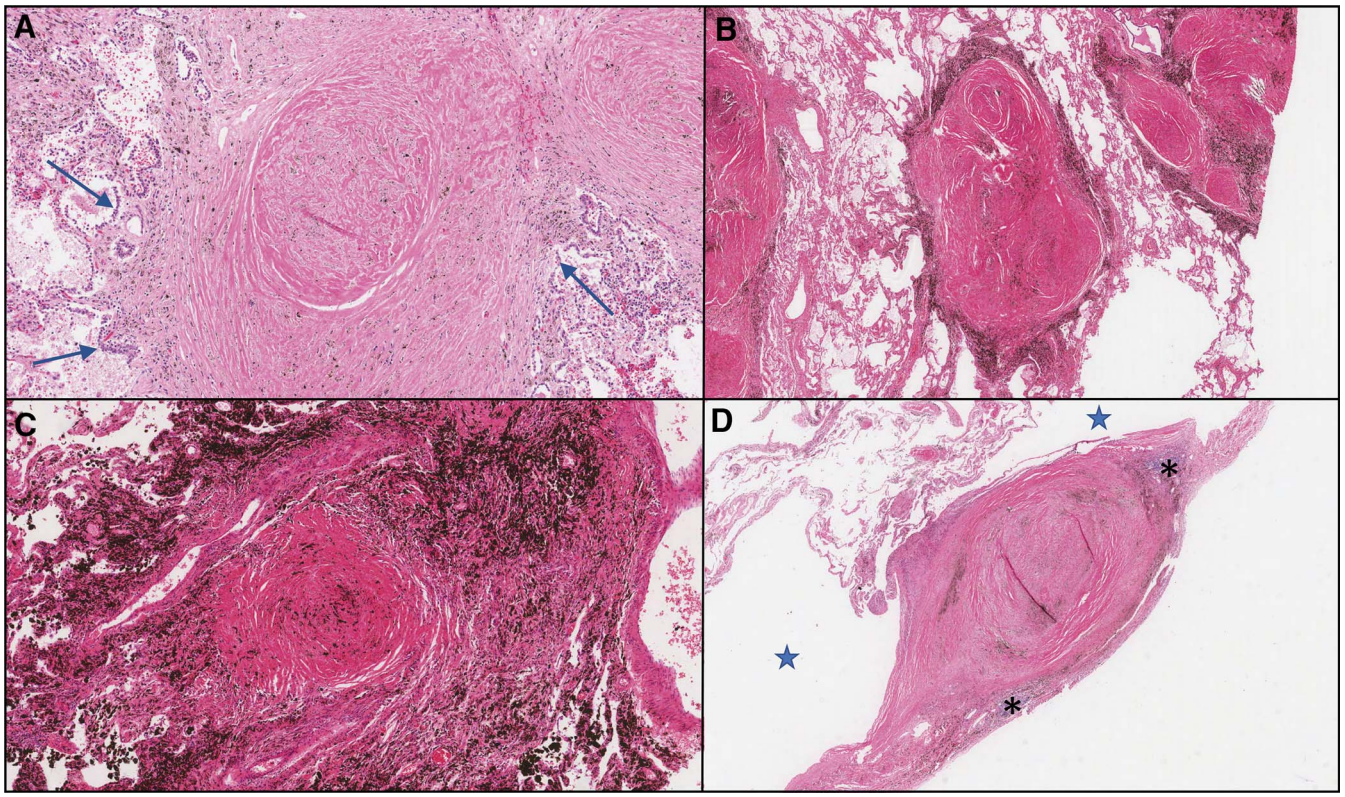

Figure 6. *Mature silicotic nodules (mild and moderate severity). A, Silica-type progressive massive fibrosis (PMF) case with numerous well-formed, mature silicotic nodules. This high-power image shows the tightly compacted concentric collagen that characterizes these lesions. The surrounding collagen is less compacted and looser in structure. Note the reactive type 2 pneumocytes lining the adjacent alveolar septa (arrows) and fusion with an adjacent immature silicotic nodule at top right of the image. B, Silica-type PMF case with mature silicotic nodules in the adjacent parenchyma. In contrast to (A), the central silicotic nodule shows tightly compacted central collagen with only a thin rim of surrounding dust. Similar mature silicotic nodules are seen to the right and to the left of the central one. C, Coal-type PMF case showing a mature silicotic nodule within the PMF lung parenchyma. This lesion shows the dense concentric collagen characteristic of the mature silicotic nodule and has become embedded in the coal-type PMF. D, A silica-type PMF case demonstrating a subpleural silicotic nodule characterized by concentric rings of dense collagen. There is patchy lymphocytic inflammation (asterisks) surrounding the nodule and severe bullous emphysema (starred spaces) (hematoxylin-eosin, original magnifications ×70 [A and C] and ×20 [B and D]).*

samples, a finding consistent with recent changes in type of dust exposure (greater quartz-containing dust component). While this may be partly explained by limitations in tissue sampling, the relative paucity of coal macules and nodules in contemporary miners was accompanied by an increase in immature and mature silicotic nodules. We also observed that the profusion of birefringent particles was inversely associated with classic coal macules and nodules, and coal dust pigment was decreased in silica-type PMF cases. Though not a differentiating feature in determining type of PMF, coal macules and nodules reflect coal mine dust exposure, and their histologic appearances should be noted in all cases.

Other Findings

Interstitial Fibrosis.—In our study, contemporary coal miners were more likely to demonstrate dust-related interstitial fibrosis, which in coal miners has been termed *dust-related diffuse fibrosis*. This finding is reported in up to one-third of coal miner lungs at autopsy.[25] DDF may occasionally resemble the UIP pattern of lung disease, including the presence of honeycomb changes[44]; however, DDF should not be mistaken for idiopathic disease.[45] Although the histology of idiopathic UIP/idiopathic pulmonary fibrosis (IPF) and the UIP associated with coal mine dust exposure may be similar, the background histologic changes of coal dust macules, nodules, and/or silicotic nodules can aid in differentiating the 2 entities. Clinically, the diagnosis of IPF requires the exclusion of other forms of interstitial pneumonia including interstitial lung disease associated with occupational exposures. DDF has significant overlap with the mixed-dust pneumoconiosis described by Honma et al.[46] Correlation with exposure history will help separate the 2 entities. The most common type of DDF noted in our coal miner lung tissue samples was bridging fibrosis, where interstitial fibrosis connects lesions of pneumoconiosis. DDF cases with RB-ILD–like fibrosis and diffuse fibrosis resembling nonspecific interstitial pneumonia may also be seen. A potential method for distinguishing RB-ILD in smokers from RB-ILD–like changes in coal miners is to count the number of birefringent particles within the pigmented macrophages.[47] Fewer birefringent particles favor smoking-related disease, while higher numbers favor coal mine dust–related RB-like disease; however, additional studies are needed to validate these findings. An additional clue to the presence of coal dust is the quality of the black pigment. Coal dust is typically black, irregular, and angular, while smokers' macrophages tend to be brown-black and finely granular. Another smoking-related disease, the recently described smoking-related interstitial fibrosis (SRIF),[48] can be differentiated from DDF by the expansion of subpleural interstitium with eosinophilic, dense, "ropey"-appearing collagen. SRIF is typically

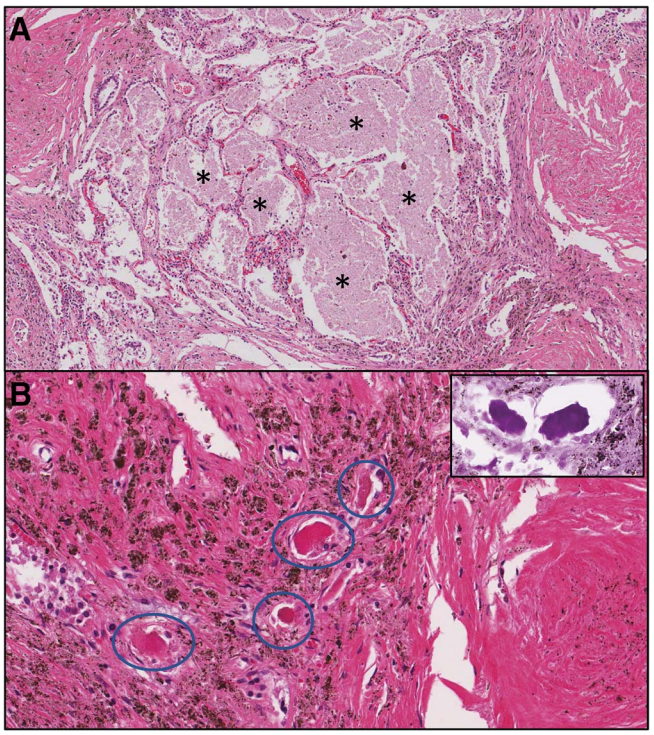

Figure 7. *Mineral dust–associated alveolar proteinosis (MDAP). A, A classic silica-type progressive massive fibrosis (PMF) case showing substantial amounts of MDAP with the typical features of alveolar proteinosis seen in congenital and secondary forms, as well as in acute lipoproteinosis associated with heavy exposure to fine particulate silica. The airspaces are filled with a granular, eosinophilic material (asterisks). Notably, the surrounding alveolar septa are relatively thin and delicate. B, Most cases with MDAP showed pockets of proteinosis within and adjacent to the PMF lesions (blue circles). A subset of cases was selected to prove that the proteinosis material was periodic acid–Schiff positive and diastase (PAS-D) resistant, confirming the diagnosis of MDAP (illustrated in the inset at the upper right) (hematoxylin-eosin, original magnifications ×100 [A] and ×10 [B]; PAS-D, original magnification ×100 [B inset]).*

an incidental finding in smokers' lungs resected for other reasons, for example, cancer. Our study found a greater prevalence of severe DDF of all types in contemporary miners. Although interstitial fibrosis is a common form of RPP, further studies regarding histologic types of fibrosis and its distribution in the lung are needed.

Inflammation.—Inflammation was a variable feature in the PMF lungs. The inflammation was of 2 types: first, a chronic type consisting of varying numbers of lymphocytes, plasma cells, and histiocytes; and second, a fibrohistiocytic type associated with immature silicotic nodules and foci of MDAP. In our study, contemporary coal miners were more likely to show substantial inflammation, which could reflect a component of autoimmunity. Notably, inhalation of crystalline silica is linked to the development of autoimmune disease.[49] Future studies are needed to explore the possible linkage.

Unusual Findings.—Our study showed rare cases with necrotizing granulomas, 1 case with a fibroelastotic lesion, and occasional cases with subpleural PMF lesions. Necrotizing granulomas may represent an infectious process, which in silica-exposed workers is often tuberculosis or other mycobacterial disease. Fungal infection such as histoplasmosis should also be considered. Necrosis in a PMF case requires the pathologist to closely evaluate special stains for organisms and suggest further clinical investigations. Rheumatoid pneumoconiosis ("Caplan syndrome") should also be considered, especially if the patient has a history of rheumatoid arthritis and the lesion(s) are mainly peripheral. Other necrotizing granulomatous diseases, such as granulomatosis with polyangiitis, should be excluded.

We found 1 case of coal-type PMF associated with extensive fibroelastosis. Although not performed in our case, elastic tissue stains may be used to highlight the disrupted elastic fibers. Subpleural fibroelastosis is a form of lung scarring and, if apical, could represent a pulmonary apical cap lesion. If the fibroelastosis is more diffuse and involves more than the upper lung zones, pleuroparenchymal fibroelastosis should be considered. Pleuroparenchymal fibroelastosis has been linked to chemotherapy and/or radiation therapy, hematopoietic malignancies, infections, postlung transplant, and as a coexisting condition with other interstitial lung diseases.[50–52] Importantly, it may also be a sequela of lung injury from fibrogenic dust exposure.[53,54] The relationship between coal mine dust exposure and fibroelastosis requires further investigation.

Subpleural PMF lesions were also identified. These lesions are usually silicotic and can coalesce into larger PMF lesions and mimic plaques ("pseudoplaques").[55] Other forms of subpleural PMF lesions may resemble rounded atelectasis pathologically and radiologically. While previously considered pathognomonic markers of asbestos exposure, our findings and those of others indicate that pleural plaques can also occur from other mineral dust exposures.[55] Regardless of appearance, the lung parenchyma adjacent to all plaquelike lesions should be examined for asbestos bodies to assess previous asbestos exposure.

Mineral Dust Small Airways Disease.—In addition to the lesions described above, contemporary coal miners may show MDSAD involving both membranous and respiratory bronchioles. The pathology of MDSAD includes thickening of the bronchiolar walls by fibrosis, muscular hypertrophy, and chronic inflammation and narrowing of the airway lumen. PLM reveals mixtures of silicates, silica, and variable carbonaceous dust within the fibrotic airway wall.[56] Cigarette smoking increases the severity of MDSAD.[56] A history of cigarette smoking or "smokers' macrophages" within the lumen of the airway and/or adjacent alveoli should be evaluated.

Differential Diagnosis of Severe Pneumoconiosis

Cases of severe pneumoconiosis in coal miners may be initially misdiagnosed clinically and radiographically as sarcoidosis, lung cancer (including rare lung neoplasms), rheumatoid nodules, or infection (eg, mycobacterial, fungal). For example, radiographically, patterns of silicosis can resemble sarcoidosis. Histologically, though, the 2 entities can be distinguished by the presence of coalescing nodules of nonnecrotizing granulomas in sarcoidosis, sometimes associated with concentric fibrosis and calcifications, while the nodules of CWP, including silica-type PMF, typically lack granulomas and demonstrate concentric nodules of lamellar collagen associated with birefringent silica and silicate particles under PLM. Birefringent material due to formation of crystals of calcium oxalate is also a common pathologic feature in sarcoidosis,[57] but this can be readily distinguished from birefringent silica and silicate particles, further underscoring the importance of PLM in the evaluation of occupational lung disease.

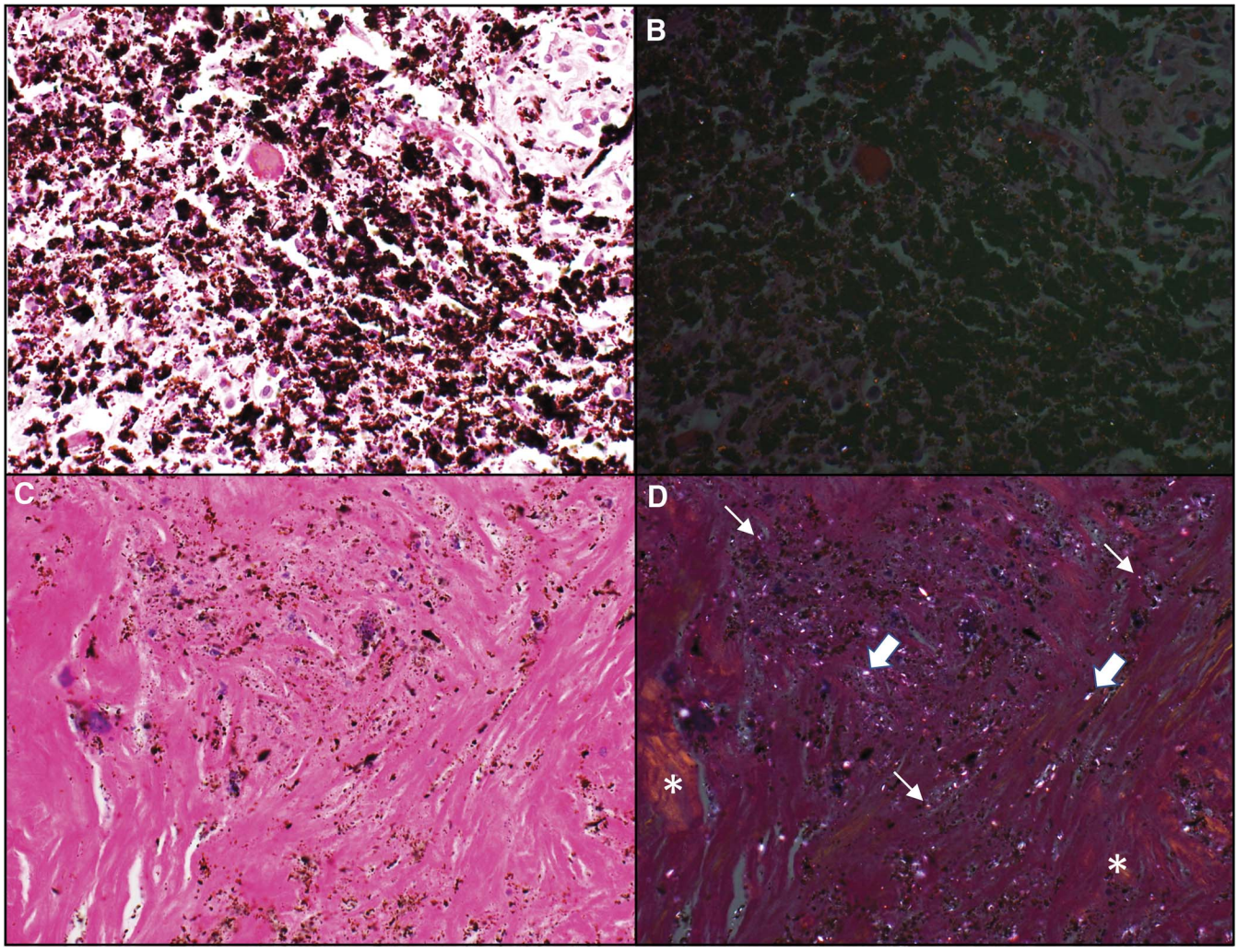

Figure 8. *Birefringent particles. A, High-power view from a coal-type progressive massive fibrosis (PMF) lesion. B, Polarized light microscopy (PLM) reveals scant birefringent particles (≤10% of the high-power field). C, High-power view of dust and collagen from a silica-type PMF lesion. D, PLM reveals abundant (>25% of the high-power field) birefringent particles. Weakly birefringent silica particles (thin arrows) and strongly birefringent silicates (thick arrows) are evident. Collagen fibers appear yellow-orange under PLM (*). Elongated fibrous particles comprise a minor component of the birefringent particles (hematoxylin-eosin, original magnifications ×400 [A through D]).*

Limitations

Our study has several limitations. First, despite having a substantial number of cases and a systematic scoring system, the sample size of historical miners outnumbered contemporary miners, limiting statistical power. *P* values are provided for interpretation, as some findings may have been observed by chance given the threshold we interpreted as statistically significant. Second, histopathologic scoring was performed with digital slide images, which, while useful for measurements, did not allow for PLM assessment of the slides. Instead, representative images of the PMF lesions (as well as non-PMF parenchyma) were examined under brightfield and PLM and photographed by 1 pathologist. The image pairs were then made available to all the pathologists for grading. Third, because cases were limited to those with PMF, assessment in some cases was constrained by the lack of non-PMF regions. Fourth, not all discordant histologic features were resolved in the consensus meetings, and in such cases median classifications were used. This may have led to underestimation of the importance of minor histopathologic features. Finally, although a 1983 report of British coal miners suggested that exposure to dust with high noncoal minerals (quartz, kaolin, and mica) causes lesions similar to silicotic nodules,[27] RPP and contemporary PMF to date are largely confined to coal miners working in central Appalachia.[7] Whether the evolution of histopathologic changes we describe are more generalized features of contemporary CWP awaits investigation from other coal mining regions and countries.

Strengths

Our study also has several unique strengths. First, the relatively large cohort of coal miners' lungs provided the basis for an updated classification of histopathologic features and comparison between historical and contemporary miners. Second, 7 expert lung pathologists, blinded to the clinical data, scored comprehensive histologic features and resolved nearly all differences in major pathologic features via consensus. Third, the standardized electronic scoring form with a priori definitions provided consistency in assessing the type and extent of important histologic

Table 1. Polarized Light Microscopy Findings of Percentage of Cases With Moderate/Severe Versus Mild Profusion of Birefringent Particles Related to Pathology Findings in Coal Miners With Progressive Massive Fibrosis (PMF)

Pathology Findings	No. Evaluated[a]	High (Moderate/Severe) Profusion of Birefringent Particles	
		No. (%)	*P* Value
All cases	85	18 (21)	—
Silica-related findings			
MDAP			.12
Absent	47	7 (15)	
Present	38	11 (29)	
Mature silicotic nodules			.17
Absent	49	7 (14)	
Present	30	8 (27)	
Immature silicotic nodules			.04
Absent	61	8 (13)	
Present	18	7 (39)	
Coal-related findings			
Coal macules			.69
Absent	12	3 (25)	
Present	68	12 (18)	
Coal nodules			.33
Absent	21	2 (10)	
Present	58	13 (22)	
PMF type			.18
Silica type	24	7 (29)	
Mixed type	26	7 (27)	
Coal type	35	4 (11)	

Abbreviations: MDAP, mineral dust–associated alveolar proteinosis; PMF, progressive massive fibrosis.

[a] Not all cases had sufficient evaluable parenchyma to classify some pathologic features.

features. The opportunity to correlate the histopathologic findings with evaluation of birefringent dust by PLM, the demographic data available,[14] and the strong correlations observed among the differing methods of assessment and findings are very rarely available and strongly support the use of such approaches to characterize evolving and emerging occupational/environmental lung diseases.

Summary

In summary, we provide an update on the pathologic characterization and classification of CWP that reflects relevant findings encompassing the recent surge in severe and rapidly progressive forms of PMF. These pathologic features are critical for understanding the complex changes in modern CWP and for recognizing the role of exposure to silica dust in contemporary coal mines. Our findings support earlier observations that silica dust exposure is an emerging cause of severe CWP. Moreover, our study separates PMF types into 3 main categories: coal-, silica-, and mixed-type. Major features associated with severe contemporary CWP include silica-type PMF, MDAP, and both immature and mature silicotic nodules. Contemporary miners also showed a relatively high load of birefringent particles by PLM consistent with silica and silicates, with a paucity of coal dust macules and nodules. Higher profusion of birefringent particles in contemporary PMF cases also correlated with the presence of MDAP and immature silicotic nodules. Historical miners more often showed histologic features of classic coal-type PMF as well as increased numbers of coal dust macules and nodules. It should be noted, though, that these are not absolute differences, and miners may have more than 1 finding and may show overlapping features in the form of mixed-type PMF, a common subtype in our study. As this contemporary form of severe CWP occurs in younger miners, is frequently misdiagnosed, and is associated with premature death and/or need for lung transplant, accurate diagnosis is important in order to understand the epidemiology of this disease and its associated comorbidities and to inform regulators, mining inspectors, and industry of the need to reduce exposures. Accurate diagnosis also is vital in supporting claims for Black Lung compensation.

The authors gratefully thank Jerrold Abraham, MD, for his invaluable assistance in reviewing and scoring the pathology slides and providing the polarized light microscopy images for the PMF cases used in this study. Many thanks also to Ann Hubbs, PhD, and Marlene Orandle, PhD, at the Health Effects Laboratory Division of National Institute for Occupational Safety and Health for assistance in reviewing and gathering materials. We also thank Lisa Litzenberger at the Department

Table 2. Percentage of Cases With Pathology Findings of Interest Associated With Historical Versus Contemporary Cases[a]

Pathology Finding	Historical	Contemporary	*P* Value
	n = 62	n = 23	
Cases with high profusion of birefringent particles, No. (%)	12 (19)	6 (26)	.56
	n = 60	n = 18	
Cases with severe interstitial inflammation, No. (%)	6 (10)	6 (33)	.03
	n = 46	n = 11	
Cases with severe interstitial fibrosis, No. (%)	9 (20)	3 (27)	.68
	n = 61	n = 20	
Cases with severe lymphoplasmacytosis, No. (%)	23 (37)	11 (55)	.20
	n = 61	n = 20	
Cases with fibrohistiocytosis, No. (%)	9 (15)	7 (35)	.06
	n = 62	n = 23	
Cases with presence of lymphoid aggregates, No. (%)	26 (42)	8 (35)	.55

[a] Not all cases had sufficient evaluable parenchyma to classify some pathologic features; number evaluated is presented for each feature.

of Pathology, University of Colorado, for her helpful imaging assistance.

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