Pleural Plaques and Their Effect on Lung Function

Libby Amphibole: Pleural Fibrosis and Its Consequences

To the Editor:

The recently published article in CHEST (September 2014) by Clark et al\textsuperscript{1} that reported no differences in pulmonary function in vermiculite miners in Libby, Montana, with pleural plaques only (PPO) raises many issues:

1. Methodology: Miners with PPO on CT scan (n = 89) were compared with a small number (n = 16) said to show no pleural thickening (PT) and 35 showing primarily diffuse PT. A publication from the Center for Asbestos-Related Disease in Libby\textsuperscript{2} uses illustrative cases to demonstrate the atypical presentation of a great deal of PT resulting from asbestos exposure: thin lamellar thickening that is not recognized on radiographs or recognized in earlier stages on CT scan and that is more consistent with diffuse than with circumscribed PT. It is likely that the small no-PT comparison group included such patients, resulting in the failure to demonstrate a difference. The group with primarily diffuse PT showed values for FVC, FEV\textsubscript{1}, total lung capacity, and diffusing capacity that were statistically significantly lower than those of the small comparison group.

2. Interpretation: The PPO group showed clearly decreased mean values for FVC (85.5% predicted), FEV\textsubscript{1} (83.7% predicted), and diffusing capacity of the lung for carbon monoxide (D\textsubscript{LCO}) (91.1% predicted) compared with the reference population from which the predicted values were calculated. It is erroneous to state that “all lung function parameters remained well within ATS/ERS [American Thoracic Society/European Respiratory Society] normal limits in the group” or that “group means were well within ATS/ERS limits of normal.”

3. Background: The effects of asbestos-related PT on pulmonary function and clinical outcome have been demonstrated in large groups with traditional exposures and in those exposed to Libby amphibole. A study by Lilis et al\textsuperscript{3} of 1,185 insulators with PT showed a statistically significant effect of PPO on FVC, as well as a much larger effect from diffuse PT. A report by Miller et al\textsuperscript{4} on 5,003 workers confirmed the effect of PPO on FVC and demonstrated a similar or greater effect on D\textsubscript{LCO}. Clark et al\textsuperscript{1} were not the first to report on diffusing capacity in asbestos-related PT.

Larson et al\textsuperscript{5} reported on a large group exposed to Libby vermiculite and concluded that restrictive spirometry was associated with PPO and correlated with its severity: “Severe (PPO) may result in respiratory symptoms.” The effects of diffuse PT were greater.

In 2004, Whitehouse\textsuperscript{6} reported “accelerated” loss of lung function in 94 Libby patients with predominant PT: 3.2% predicted per year for vital capacity, 2.3 for total lung capacity, and 3.3 for D\textsubscript{LCO}. Black et al\textsuperscript{7} illustrate the rapid functional and clinical progression and prominence of chest pain in Libby patients.

In conclusion, the article by Clark et al\textsuperscript{1} reporting on a small number of patients with PPO does not contravene the increasing recognition of Libby amphibole as a unique asbestos exposure that can result in progressive respiratory embarrassment from PT.

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FINANCIAL/NONFINANCIAL DISCLOSURES: The author has reported to CHEST that subsequent to the submission of this article he was requested, and agreed, to serve as a limited consultant to the Center for Asbestos Related Disease in Libby, Montana.

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References

Response

To the Editor:

We appreciate Dr Miller’s interest in our study recently published in CHEST. Although the number of Libby vermiculite miners with normal high-resolution CT (HRCT) scans is relatively small, the statistical analyses of our data were scientifically robust and independently reviewed. Our analyses were unable to detect statistically significant mean lung function differences between the miner group with pleural plaque (PP) only and the miner group with normal HRCT scan (NCTS) studies, even though there was enough power to detect statistically significant mean lung function differences between smaller miner groups (PPs with coexisting interstitial fibrosis and other HRCT scan abnormality [OCTA]) and the NCTS reference group. Information contained within the 95% CI for comparison of the miner group with PPs only with the NCTS reference group indicates that we should not reject the null hypothesis. Tukey analysis was also used to minimize type 1 error. Thus, our analysis supports the conclusion that PPs alone have no significant effect on lung function in Libby vermiculite miners.

Our study also demonstrated a statistically significant reduction in total lung capacity among miners with both PP and interstitial fibrosis on HRCT scan in comparison with miners with NCTS. These findings are consistent with previous reports, including 2013 publication by Miller et al, which suggest that lung function decrements reported among asbestos-exposed individuals with PP on chest radiographs are caused by coexisting parenchymal fibrosis, which is not detectable by chest radiograph, and not by the PP per se. This is the most likely explanation of the difference in outcomes between our study and the 1991, 2004, 2012, and 2013 studies cited by Dr Miller, all of which used chest radiograph findings rather than more sensitive HRCT scan findings as used in our study. As referenced in our article, it has also been reported that HRCT scan is much more sensitive than chest radiograph in detecting PP and in distinguishing PP from pleural fat deposits. In this regard, our use of HRCT scan provides a more accurate assessment of associations between radiographic findings and lung function in comparison with studies that use chest radiographs. Furthermore, no Tukey analysis was reported in any of the four cited studies, which makes it possible that the statistical analyses in these studies had had a greater type 1 error than was present in our study.

Dr Miller references a 2014 publication by Black et al, which reports five cases of extensive, painful, rapidly progressive pleural thickening among individuals exposed to Libby amphibole asbestos. We agree with Dr Miller that these findings are consistent with diffuse pleural thickening (DPT) and not with PP. In view of the extensive nature of their DPT, it is not surprising that these individuals had restrictive impairment. Furthermore, the chest pain experienced by these individuals could also cause “splinting” of the chest wall, limit chest wall excursion, and, therefore, contribute to the observed restrictive ventilatory impairment. Unfortunately, no pleural biopsies were performed, and, therefore, no correlation between the CT scan findings and the histopathologic characteristics of the painful, rapidly progressive DPT was reported. However, in comparison with these five cases, none of the miners in our study with NCTS, PP only on HRCT scan, or PP with interstitial fibrosis on HRCT scan had any evidence of DPT. We can find no scientific evidence that HRCT scan is unable to detect early, diffuse, lamellar pleural thickening that is extensive enough to cause restrictive ventilatory impairment, as suggested by Dr Miller. Additionally, the case series reported by Black et al is a descriptive study by design. It is important to note that descriptive studies do not have a comparison group and are unable to assess associations. Therefore, since the results of our study are based upon a comparison of miners with isolated PPs alone on HRCT scan to miners with NCTS studies, the five cases reported by Black et al have no scientific relevance to our conclusion that asbestos-related PPs alone have no significant effect on lung function in Libby vermiculite miners.

Dr Miller refers to a group of miners “primarily with DPT” in our study. No such group was reported in our article. Of the 35 miners in the OCTA group, most had multiple HRCT scan abnormalities, and only nine had evidence of DPT. The OCTA group was included to account for all miner data obtained in the study and had no bearing on our study conclusion; the number of OCTA group miners with each specific constellation of HRCT scan abnormalities was not reported in our article. Therefore, Dr Miller’s assertion that we had a miner group “primarily with DPT” is incorrect. In our article we refer to data in our study, as well as those in a previous study by Clin et al, in which the mean percent predicted values of all reported lung function measurements for subjects with PP alone on HRCT scan were...
well above the lower limits of normal and, therefore, well within limits for being interpreted as normal by current American Thoracic Society/European Respiratory Society guidelines.\textsuperscript{1,3} We respectfully disagree with Dr Miller’s assertion that our interpretation of these data are “erroneous.” In our article, we state that we are the first, to our knowledge, to investigate the effects of PP on the lung function of Libby vermiculite miners by using HRCT scanning, plethysmography determined lung volumes, diffusing capacity of the lung for carbon monoxide, and ratios of diffusing capacity of the lung for carbon monoxide, and alveolar volume. We did not state that we were the first to report on diffusing capacity in asbestos-related pleural thickening, as Dr Miller implies. Although we appreciate Dr Miller’s interest in our study, we must respond to these assertions by stating that they are unsubstantiated and incorrect.

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FINANCIAL/NONFINANCIAL DISCLOSURES: The authors have reported to CHEST the following conflicts of interest: Ms Clark received a graduate student research grant from Health Network America for the collection and analysis of medical surveillance data from the LMP. Funding for this research grant was provided to Health Network America by W. R. Grace and Co. Dr Goodman is a Principal at Gradient Corp, an independent environmental and risk science consulting firm, in Cambridge, Massachusetts. Dr Zu is a research associate at Gradient Corp. Through a contract with Gradient Corp, Drs Goodman and Zu have served as scientific consultants to W. R. Grace and Co on issues related to asbestos exposure and asbestos-related health risks. They both contributed to the data analyses reported in this manuscript with funding received through the Gradient consulting contract with W. R. Grace and Co. W. R. Grace and Co has recently provided research funding to Gradient Corp for a preliminary weight-of-evidence study related to associations between PPs and lung function. Dr Goodman has served as an expert witness on cases involving chrysotile asbestos and cancer risk and has received funding from Tucker Ellis & West LLP for the preparation of scientific manuscripts regarding radiation, mesothelioma, and lung cancer. She previously received funding from the National Cancer Institute as a Cancer Prevention Fellow. Dr Flynn is an independent physician contractor for Health Network America, a health-care consulting company, in Eatontown, NJ. He served as Medical Director of the LMP from January 2001 to January 2013, as a Health Network America employee. Health Network America received fees from W. R. Grace and Co for providing administrative services to the LMP. Dr Flynn participated in all public comment sessions for the Environmental Protection Agency Toxicological Review of Libby Amphibole Asbestos in 2011 and 2012, in his capacity as Medical Director of the LMP. Dr Karmaus has received no funding for his work on this project and has no potential conflict of interest; he has received research funding from the National Institutes of Health for work on other projects in collaboration with Ms Clark and Dr Mohr. Dr Mohr has served as a research consultant to Exponent and Health Network America, scientific research and consulting firms, which received funding from W. R. Grace and Co for research and scientific consultation on asbestos-related health risks. He has also received funding through a research contract with Gradient Corp for a literature review and preliminary weight-of-evidence study related to associations between PPs and lung function. He has submitted public commentary reports to the Scientific Advisory Board of the US Environmental Protection Agency on the Draft Toxicological Review Pertaining to Libby Amphibole Asbestos (2011) and the Association Between Localized Pleural Thickening (Pleural Plaques) and Lung Function; both reports were submitted in his capacity as a research consultant to Exponent, which received funding from W. R. Grace and Co for this work. Dr Mohr has received research grant funding from the National Institutes of Health, the National Cancer Institute, the US Department of Energy, the Agency for Healthcare Research and Quality, the Health Resources and Services Administration, the South Carolina Universities Research and Education Foundation, and the North Atlantic Treaty Organization for work on other research projects. He has served on scientific advisory boards for Marine Polymer Technologies, Inc and Entegro. The authors wish to report that W. R. Grace and Co operated the Libby Vermiculite mine from 1963 to 1990.

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