Histopathologic Insights into Distal Lung Injury and Inflammation following Military Deployment

It has been more than a decade since the 2011 publication of the sentinel report of constrictive bronchiolitis in Iraq and Afghanistan deployed military personnel (1). Since then, a handful of studies have examined and further characterized lung histopathologic abnormalities in this population, and even fewer have addressed mechanisms of lung disease (2–5). A number of epidemiologic studies have described the spectrum of post-deployment respiratory diseases and sought to explore associations between inhalational hazards (e.g., burn pit emissions, desert dust, and diesel exhaust particulate matter) and new-onset asthma and distal lung disease (bronchiolitis). However, lack of systematic, quantitative, and individual level exposure assessment during military deployment to Afghanistan, Iraq, and other Southwest Asia (SWA) locations have impeded these research efforts (6). Despite these limitations, there is mounting evidence supporting the link between military deployment and respiratory symptoms and disease (7, 8). Recently, the Department of Veterans Affairs acknowledged these exposure–disease linkages and issued a presumption connecting asthma, chronic rhinitis, and sinusitis diagnosed within 10 years of military service in veterans with particulate matter exposure during SWA military deployment (9).

Although evidence-based treatment is available for upper airway disease and asthma, there is no currently approved pharmacotherapy for distal lung diseases such as post-deployment constrictive bronchiolitis. Treatment recommendations require further understanding of disease pathogenesis and progression. Gutor and colleagues (pp. 260–270) take an important step in this direction as discussed in this issue of the *Journal* (10).

In an effort to identify distal lung abnormalities that distinguish constrictive bronchiolitis (referred to by the authors as "ConB") from small airways pathology seen in other diseases, Gutor and colleagues conducted a histomorphometric analysis of the small airways in lung biopsy samples from previous SWA-deployed military personnel, positive controls with sporadic constrictive bronchiolitis, chronic obstructive pulmonary disease patients, and healthy controls. They also performed gene expression profiling in a subset of SWA-deployed patients compared with both diseased and healthy controls to characterize the immune and inflammatory phenotype in affected soldiers. Their findings are consistent with those of earlier studies that describe a lymphocyte-predominant inflammatory phenotype with evidence of T-cell activation (2, 5).

Merits of this study include systematic direct lung histopathologic evaluation with semi-quantitative assessment of inflammatory cells and measurements of lamina propria, smooth muscle adventitia thickness, as well as collagen and elastin content in the small airways of previously deployed patients compared with controls. Gene expression analysis provides further insights into possible disease mechanisms, with upregulation of mainly Th-1 type pro-inflammatory pathways (e.g., NF-κB, Toll-like receptor, and T-cell signaling). However, choice of the term "ConB" to describe the lung histopathologic abnormalities in affected soldiers is unfortunate. While constrictive bronchiolitis is often found, these and other investigators describe a spectrum of distal lung abnormalities (e.g., lymphoid aggregates, granulomatous pneumonitis, emphysema) affecting multiple lung compartments in addition to distal small airways (3, 5).

Importantly, the Gutor study demonstrates the utility of lung biopsy in advancing our understanding of SWA deployment-related distal lung disease and informs vital future research directions related to treatment and disease prognosis. While biopsies are not without risk, understanding pathogenesis and treatment of new disease entities often is informed by histopathology. This is particularly true for unexpected or unexplained exposure-related lung diseases. For example, the devastating resurgence in rapidly progressive and severe pneumoconiosis in younger Appalachian coal miners has been linked definitively to exposure to crystalline silica based on lung histopathologic and mineralogical analysis (11). Examination of lung biopsies in recent international silicosis outbreaks has shown overlapping features of acute silicoproteinosis and accelerated silicosis in a particularly aggressive form of silicosis in artificial stone workers (12). Some cases were mistaken clinically for sarcoidosis until lung biopsy revealed artificial stone-associated silicosis (13). Similarly, lung biopsy played a vital role in establishing the link between World Trade Center dust exposure among first responders and firefighters and subsequent cases of granulomatous pneumonitis (14, 15). For indeterminate cases of possible usual interstitial pneumonia pattern on chest imaging, surgical lung biopsy may provide diagnostic clarity when suspicion for chronic fibrotic hypersensitivity pneumonitis exists (16). Though there are few reports of lung biopsy findings in workers with severe flavoring-related fixed airways obstruction, a pattern of granulomatous pneumonitis and bronchiolitis similar to that seen in SWA-deployed soldiers has been described (17). All of these studies with histopathologic correlations implicate a role for innate and adaptive immunity in particular exposure-related lung diseases

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and point to important avenues for future investigation. Crucially, as we begin to understand more about deployment-related respiratory disease, lung histopathology when available, coupled with advanced mineralogic techniques, may not only aid in understanding disease pathogenesis and prognosis but also may help inform future exposure prevention efforts. ■

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