

Interstitial Lung Disease and Mediastinal Lymph Nodes: A Computed Tomography–based Biomarker beyond Nosological and Etiological Borders?

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ILD and mediastinal lymph nodes: A CT-based biomarker beyond nosological and etiological borders?

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To the editor:

We read with great interest the article by A Adegunsoye *et al.* (**1**) recently published in the AJRCCM. Using a rigorous multi-validated protocol, the authors demonstrate that mediastinal lymphadenopathy (MLA) is a strong predictor of clinical outcomes in interstitial lung diseases (ILD), considered as a unique heterogeneous entity including IPF, IPAF, CHP, CTD-ILD and Unclassifiable ILD. Nonetheless, if the results on the strong prognostic value of MLA on survival when all sub-entities are mixed (Figure 1 (**1**)), could have important implications for patient stratification in the future, considering all types of ILD together may indeed reach its limits when interpreting the results on plasmatic biomarkers. For example, based on their results and those of ongoing trials in IPF, the authors suggest that IL-6 might be protective in fibrotic ILD (**1**). This statement might be tempered, especially when considering CTD-ILD, since IL-6 may constitute a therapeutic target in Scleroderma-associated ILD, with promising results of Tocilizumab on pulmonary involvement in a recent clinical trial (**2**). From a pathogenesis and nosological viewpoint, separating each ILD subgroup may therefore remain relevant.

Beyond prognostic and therapeutic considerations, Adegunsoye and colleagues' results may have far-reaching heuristic consequences, and raise the issue of the precise etiology and pathogenesis of MLA in ILD. In their work, obvious causes of MLA were carefully ruled-out since sarcoidosis, drug-toxicity-related ILD and cancers were excluded. Nonetheless, although age and gender were included in the multivariable Cox regression model (Table 2(**1**)), the possible role of chronic heart failure as a concurrent etiology of MLA (**3**) as well as a cause of all-cause hospitalization and/or respiratory hospitalization and/or death, cannot be completely excluded. This hypothesis is supported by the significant difference ($p=0.028$) in the prevalence of coronary heart disease between patients with and without MLA (Table 1(**1**)). This is particularly true when considering the association of MLA with higher pulmonary artery diameter, higher Aorta diameter, male gender, older age and tobacco use.

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Although we do not assume that heart failure alone may explain the strong prognostic value of MLA in ILD, exploring the association of MLA with cardiac biomarkers such as NT-ProBNP levels (**3**) and their respective prognostic values may help to clarify this issue.

From an etiologic viewpoint, this specific focus on MLA may bring back into light neglected causes of ILD with MLA, such as dust exposures. No mention is made of pneumoconiosis in Adegunsoye's work. The higher prevalence of MLA in men (Table 1(**1**)), in addition with the well-known association between occupational dust exposures and male gender, also highlights this issue. Recent studies have pointed out that the prevalence of crystalline silica exposure in CTD-ILD might be under-evaluated (**4**). There is growing interest for the involvement of environmental airborne contaminants in ILD of unknown etiologies such as IPF (**5**) but also in CTD-ILD (**4**) or other fibrotic ILD like pulmonary alveolar proteinosis (PAP) with fibrotic features (**6**). Beyond size, location or number, giving a thorough description of MLA, with a specific attention paid to density or calcifications, may offer new insights into the complex relationship between exposure to airborne contaminants and ILD. Histological considerations on MLA in ILD may also help to clarify the immune processes at stake. As recently suggested about PAP of autoimmune origin, *dysimmune* is not synonymous with *idiopathic* (**6**). Therefore, further studies are needed to better understand the specific etiologies of MLA in ILD of unknown origin. In the end, this could help to refine the current nosological classification of these diseases, and possibly improve the search for a proper cause leading to potential efficient preventive measures.

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