TITLE: Uncovering environmental signatures in interstitial lung disease using scanning electron microscopy with energy-dispersive X-ray spectroscopy

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Introduction: Interstitial lung disease (ILD) comprises a heterogeneous group of inflammatory and fibrotic disorders, many of which remain of unknown etiology. The contribution of occupational and environmental exposures may be underestimated as current assessment relies largely on self-reported history. Scanning electron microscopy with energy-dispersive X-ray spectroscopy (SEM/EDS) enables the direct detection and characterization of inorganic particles in lung tissue and bronchoalveolar lavage (BAL) samples. This study aims to assess particle burden and composition across different ILD subtypes and to investigate their associations with radiological progression.

Methods: We retrospectively analyzed 34 patients with a self-reported occupational and/or environmental exposure who underwent lung biopsy and/or BAL for diagnostic purposes and subsequently SEM/EDS at our University Hospital between May 2023 and April 2026. Particle presence or absence was defined according to the detection or non-detection of a pathological inorganic particle burden. Associations between SEM/EDS results and 12-month radiological progression, where applicable, were evaluated using Fisher's Exact test.

Results and conclusions: Considering the overall population we found the presence of at least one inorganic component in 31 patients out of 34 (91%). Silica was the most frequently detected component, being identified in 21 patients (62%); calcium was also frequently observed, with 19 out of 34 patients (56%). Among the different types of silicates, aluminum silicates were identified in 13 patients (38%), magnesium silicates were found in 7 patients (21%), calcium silicates were detected in 4 patients (12%) while iron silicates were present in 3 patients (9%). In 15 patients (44%), we identified other silicates, which we grouped as mixed silicates. In 13 patients (38%), at least two types of silicates were found in combination. In non-pneumoconiosis cases (n = 24), aluminum and magnesium silicates were strongly associated (p = 0.002), with magnesium always co-occurring with aluminum silicates. Calcium was associated with 12-month radiological progression in the overall cohort (p = 0.007), although this finding should be interpreted cautiously, as pulmonary calcium deposition may also reflect an endogenous pathological process. Excluding pneumoconiosis, silica was more frequent in non-IPF (n=19) than IPF patients (n=5) (p = 0.01), although IPF patients did not report occupational or environmental silica exposure. In conclusion, SEM/EDS revealed at least one inorganic component in almost all patients, particularly silica, that was more frequent in non-IPF patients. The presence of calcium was associated with radiological progression at 12 months. To the best of our knowledge, this is the first study to systematically apply SEM/EDS to a cohort of patients with ILD. Integrating mineralogical analysis into multidisciplinary evaluation of ILD may help uncover previously unrecognized exposure signatures. These exploratory results support mineralogical analysis in ILD, but require validation in larger cohorts.