LAM is another small airway disease: lessons from microCT

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Among interstitial lung diseases, the presence of cysts is a characteristic of lymphangioleiomyotosis (LAM). Insight was gained thanks to genetic studies which unravelled the involvement of the tuberous sclerosis complex (TSC)-mTOR pathway. Accordingly, both sirolimus (an mTOR inhibitor) and everolimus (an inducer of autophagic flux) gained approval in the treatment of LAM [1]. Now the question is how and when these drugs should be best initiated. In a way very similar to what currently stands in COPD, the earliest looks the best. Intuitively, the main issue is then to justify what would be the most appropriate outcome to improve and/or to prevent. Understanding the natural history of the disease would then allow for early interventions based on early events.

Classically, this kind of clinical science is mostly driven by the design of pivotal clinical trials. Micro-computed tomography (microCT) is surprisingly coming to this ground. Using highly sophisticated both pathological and radiological methods efficiently conjugated to assess micro-anatomy of LAM explant lungs, S. Verleden and colleagues have deciphered the mechanisms involved in the progression of the disease. In a way that may not have been achievable using conventional pathology, they have been able to reproduce what was found in seminal papers dedicated to COPD [2]: a strong loss of small airways is a feature of LAM. The missing link between lymphatic vessel dysfunction and this loss of small airway is moreover addressed in the paper released in this issue of the *European Respiratory Journal* [3]. Cysts full of HMB45 positive cells develop in the immediate neighbourhood or in the wall of small airways and progressively collapsed them. The sequence of events is completed by the observation of airway wall thickening, and the presence of airway exudates that may contribute to their definitive plugging, precipitating their loss. Again recalling what has been shown in COPD and more recently in IPF [4], but involving completely distinct mechanisms, these lesions are match well with parenchymal destruction, suggesting here again that the first may precede the second. Because together is always better than alone, the reviewing process fed ideas for adding analysis from complimentary scanning electron microscopy. These newly generated data also provide new insight by showing the vascular component of the disease that seems to follow the same mechanistic process.

How do we take advantage and translate these new findings for treating patients?

Given these new insights, we may decide to treat LAM patients based on the presence of small airway disease, as early as possible. Diagnostic issues will be potentially solved by the wider use of high-resolution

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CT combined with serum VEGF-D assessment as simpler diagnostic tools, potentially limiting the need for lung biopsies [5]. Determining the presence of small airway disease may require up-to-date physiological assessment and/or expiratory CT slices, reinforcing the need for reference/expert centres. Preventing accelerated lung function decline would then logically become the main and primary outcome of the treatment, largely earlier than a fall in diffusing capacity of the lung for carbon monoxide, for example, together with the prevention and/or cure of angiomyolipoma and other manifestations of lymphatic dysfunctions.

Lung microCT appears to be a new research tool, demonstrating its complementary value when associated with more conventional paraffin-embedded tissues analysis. All these recent findings advocate for widening microCT use and availability in pathological facilities for improving insights provided by current routine procedures.

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