Lung pathology for the clinician: a comprehensive approach

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The new series "Pathology for the clinician" will address current concepts of interest in respiratory medicine http://ow.ly/Z7II30bBw9E

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The articles by Ghigna *et al.* [1] and Bubendorf *et al.* [2], in this issue of the *European Respiratory Review* (*ERR*), are the first two out of six reviews that form the series "Pathology for the clinician". This series has been initiated in order to draw a comprehensive picture of pathophysiology and pathology in current concepts of interest, with articles on pulmonary hypertension (PH) in pulmonary parenchymal disease, on the role of macrophages in interstitial lung disease, and on ageing of the lung. Another, more clinical, intention of this series has been to provide state-of-the-art strategies to consolidate the interactions between respiratory physicians on one side and technical specialties on the other (the latter mostly work with biological material obtained by the former). With this aim, there will be articles on clues and pitfalls in granulomatous diseases of the lung, on unclassifiable interstitial lung disease, and on diagnostic difficulties in small biopsies and cytological specimens for nonsmall cell lung carcinoma. It goes without saying that the series cannot and is not meant to cover all subjects that matter in respiratory medicine; it should rather be seen as a potpourri of (important) examples that help understand: 1) the transdisciplinary approach to lung disease, and 2) the wide range of currently used diagnostic strategies/possibilities that can be reached if pathologist and clinician work consciously hand in hand.

The first article in this series, by Ghigna *et al.* [1] in this issue of the *ERR*, is a comprehensive review on PH in patients with parenchymal lung disease. This is of major interest, since the last decades have seen important scientific progress and therapeutic innovation in the domain of PH. Historically, pulmonary arterial hypertension (PAH), formerly known as primary pulmonary hypertension, has been in the focus of research interest. Despite their "orphan disease" tag, most insight has been gained into its "primary" forms, idiopathic PAH and heritable PAH, *e.g.* with the identification of several genetic factors, such as mutations in the *BMPR2*, *ACVRL1*, *KCNK3*, *CAV1*, *SMAD9* and *BMPR1B* genes [3, 4]. On the therapeutic level, many new drugs, such as phosphodiesterase type 5 inhibitors, endothelin antagonists and diverse intravenous, subcutaneous and oral prostanoids, have been approved; in consequence, management and prognosis of patients suffering from PAH has changed [5]. Lately, research interest has expanded to other forms of PH, in particular chronic thromboembolic pulmonary hypertension (group 4 of the Nice classification) and hypoxia-/parenchymal disease-related PH (group 3 of the Nice classification), with true therapeutic advances in the former (stimulator of soluble guanylate cyclase) [6, 7]. At face value, it would

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seem that parenchymal disease-related PH (group 3) is less of a pathophysiological mystery, since there appears to be a coherent "grip", the underlying disease. In reality, however, things are more complex, since chronic obstructive pulmonary disease (COPD) patients, for instance, can display a comparable degree of emphysema yet can have normal haemodynamics or develop mild or even severe PH (formerly called out-of-proportion PH). Hitherto, neither the biology nor the anatomical/histological correlation of this varying "reaction" of the lung vasculature to the underlying disease has been well understood or sufficiently determined, despite a recent increase of scientific papers addressing the field [8]. With respect to the irreversibility of diseases such as emphysema or idiopathic pulmonary fibrosis (IPF) (to name another example of parenchymal disease frequently associated with PH) and the well-established outcome-obscuring impact of PH in these conditions, a fresh focus on the vascular component of parenchymal disease and hypoxic conditions appears mandatory, also with regard to innovations in specific medical therapy. The need for this focus is all the more evident when taking into account the high prevalence of pulmonary parenchymal diseases, clearly leaving behind the academic peculiarities of orphan disease.

Concerning oncology, the role of the pathologist has substantially changed these past years, since it has become clear that the most promising future of cancer therapy relies on personalised approaches, demanding individual profiling of target genes or antigens. In addition to a precise visual diagnosis, where immunohistochemical staining is utilised as an accessory to the morphological assessment, the job description of a pathologist now includes well-defined handling procedures and tumour-banking of the human tissue. With regard to pulmonary oncology, the handling of small samples, obtained by techniques such as endobronchial ultrasound-guided transbronchial needle aspiration or computed tomography-guided transparietal pulmonary biopsies, is not always simple and interpretation of therapeutic target markers with immunohistochemical, cytogenetic and other molecular techniques can be challenging. Despite the existence of large onco-biological platforms, which are frequently part of (or at least associated with) the pathology department in university hospitals, it is becoming more and more clear that, in the long term, these highly specialised and very well equipped centres will continue to serve more as the spearhead of therapeutic research and adjustment, in other words as the "R&D department" of onco-pathology. In contrast, validated knowledge about gene mutations or gene variations will be translated, if possible, into more cost-effective methods such as simple immunohistochemical detection of the varying or absent gene product (*e.g. ALK*, *ROS1*, *PD-L1*). That said, even more sophisticated methods, such as fully automated and miniaturised mRNA panel detection of mutations (*e.g. KRAS*, *BRAF*, *EGFR*), have been recently developed for pathology departments of smaller hospitals and even private practice [9]. The second article of the series "Pathology for the clinician", by Bubendorf *et al.* [2] in this issue of the *ERR*, can be read as a practical guide to modern pulmonary onco-pathology, comprising an in-depth review of the current knowledge of molecular biology in this area.

This series will also include four more articles that will appear in the upcoming issues of the *ERR*. Ohshimo *et al.* [10] will provide a comprehensive review on differential diagnosis of granulomatous lung diseases, a traditionally challenging field for clinician, radiologist and pathologist alike, also discussing new techniques (like cryobiopsy) that potentially could improve the diagnostic accuracy. Macrophages are a frequent incidental finding in lung biopsies performed for interstitial lung diseases, but occasionally they are clinically significant (*i.e.* the reason for which the biopsy was performed). Rossi *et al.* [11] will review, from the pathologist's perspective, the main pulmonary diseases caused by the accumulation of macrophages and dendritic cells, providing several practical morphological clues useful to manage this complicate matter. A review for this series is also planned that will tackle the important issue of unclassifiable interstitial lung diseases, a controversial concept but not an exceptional event in clinical practice, in a significant proportion of cases simply due to the impossibility of obtaining a surgical lung biopsy. Senescence is emerging as an important element in the pathogenesis of several lung diseases, including COPD and IPF, and a further article in this series will review the intriguing relationship between COPD and ageing of the lung.

In our opinion, this series on "Pathology for the clinician" largely meets the goals for which it was planned. We are indebted to Sergio Harari for providing the opportunity to edit this series, and we congratulate the authors for their outstanding contributions. We hope you will enjoy their efforts.

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