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EDITORIAL: CLINICAL ASSEMBLY

Smoking-related lung diseases: a clinical perspective

Clinical Assembly contribution to the celebration of 20 years of the ERS

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The cause–effect relationship between a history of cigarette smoking and chronic obstructive pulmonary disease (COPD), emphysema and lung cancer is embedded in a heritage of older studies, although new approaches, classifications and imaging techniques and new treatments have been proposed over the past two decades. In recent years, new players in the field have been added: smoking-related interstitial lung diseases (SR-ILDs) now comprise a number of different presentations, while recently a new entity has been highlighted, *i.e.* combined pulmonary fibrosis and emphysema (CPFE). This editorial will review the noticeable progress made over the past 20 yrs in our understanding and characterisation of the vast array of abnormalities and clinical pictures pertaining to the respiratory system associated with tobacco smoking.

Great efforts over the years in the diagnostic and therapeutic classification of chronic bronchitis and emphysema resulted in the umbrella term of COPD being adopted. The seminal paper, published in 1995, defined COPD as a condition characterised by ''reduced maximum expiratory flow and slow forced emptying of the lungs; features which do not change markedly over several months. Most of the airflow limitation is slowly progressive and irreversible'' [1]. This was one of the first guideline papers for COPD and it still retains its place in the literature, being the single most quoted article ever published in the *European Respiratory Journal*!

Imaging techniques have incredibly widened our ability not only to ''see'' but also as a consequence to better categorise lung disease, including those that are smoking related. High-resolution computed tomography (HRCT) is highly sensitive in the detection of abnormalities in the lung parenchyma and airways. In advanced COPD, airflow limitation is reflected by airway narrowing, airway deformity and extent of emphysema. The degree of airway involvement in COPD can vary greatly for the same degree of airflow obstruction, depending on the type of emphysema smokers develop, with centrilobular emphysema showing more severe inflammatory changes and narrower airways than panlobular emphysema [2]. HRCT of early centrilobular emphysema shows tiny centrilobular areas of low attenuation with ill-defined borders. With enlargement of the dilated airspace, the surrounding lung parenchyma is compressed, which enables observation of a clear border between the emphysematous area and the normal lung. In panlobular emphysema, HRCT shows either panlobular low attenuation or ill-defined diffuse low attenuation of the lung [3].

Emphysema in its panlobular form is considered to be the characteristic manifestation of the destructive activity that smoke can induce against alveolar walls and septa. Panlobular emphysema is the hallmark of lung disease, particularly in subjects with a history of smoking, and with α_1-antitrypsin deficiency (AATD). AATD is probably the most frequent, albeit rarely recognised, monogenic condition throughout the world. This has been the topic of many studies, among which those addressing the never-ending question on the ability of augmentation therapy (or replacement of the levels of endogenous α_1-antitrypsin with weekly infusion of exogenous α_1-antitrypsin) to slow the loss of pulmonary function in patients with AATD [4]. European Respiratory Society experts also participated in the clinical guidelines for AATD, which were issued along with the American Thoracic Society in 2003 [5]. Emphysematous patients may often be referred for surgical procedures, such as lung volume reduction surgery (LVRS). Feasibility and safety of endobronchial one-way valve placement during bronchoscopy in severe homogeneous emphysema have been evaluated over the past years, with the aim of reducing lung hyperinflation and thus improving pulmonary function and exercising tolerance, similarly to LVRS [6].

The role of rehabilitation is now well established as an evidence-based nonpharmacological approach in the management of COPD and its scientific value is reported in all guidelines cataloguing the management of the disease [7]. The evidence base is accumulating for other chronic disabling respiratory diseases, for example ILD [8], in which the initial response to rehabilitation is encouraging. The principles of rehabilitation apply across the spectrum of chronic respiratory diseases and the format of the intervention is well described. The point at which rehabilitation becomes appropriate has largely been confined to individuals with stable COPD, Medical Research Council (MRC) dyspnoea scale grades 3–5, and should not be denied to patients with chronic respiratory failure (CRF) due to COPD, as it was shown that rehabilitation in these patients is equally effective as in patients with COPD but without CRF [9]. There is also some evidence that rehabilitation is valuable for MRC grade 2 patients [10],

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although the precise format of the intervention for patients with milder disease has yet to be confirmed, with a number of schemes being proposed, ranging from a simple and brief opportunistic advice to increase physical activity, through to formal rehabilitation. The potential value of an earlier intervention was further highlighted, describing a disproportionate decline in exercise capacity and physical activity across all COPD stages, compared to decline in spirometry [11].

Tobacco smoking is by far the most important factor in the occurrence of lung cancer. Most new diagnoses of lung cancer are made at an advanced disease stage and >50% of these patients will have involvement of the central airways [12]. This can be in the form of bulky endobronchial disease, endobronchial extension or extrinsic compression of the airways by the tumour. Shortness of breath, haemoptysis and cough are often the complaints that bring patients to clinicians. Interventional pulmonology represents an option that should be available, at least in national reference centres, for many respiratory patients, including patients with smoking-related lung diseases, such as lung cancer. Some of these patients may benefit from endobronchial intervention as part of the management of their disease. Many studies not only demonstrate improvement in clinical symptoms and quality of life, but also suggest increased overall survival with the use of endobronchial management techniques. Not all endobronchial disease causes complete obstruction of the airways. Sometimes patients have partial obstruction, which often has a less severe symptom complex. As these patients enter treatment programmes, the endobronchial component of their disease, in response to these treatments, can lead to more complicated concerns. External-beam radiotherapy can induce endobronchial inflammation and swelling, further compromising the airways. Radiation or chemotherapy can lead to necrosis of the endobronchial component of the cancer. The inflammation and necrotic tissue can cause further airway damage by inducing airway obstruction, lung collapse and possible post-obstructive pneumonia. Therefore, endobronchial techniques should be considered throughout the management of lung cancer patients [13]. When all management options have been used, end-stage patients will often develop compromise of their airways as the cancer continues to progress. Endobronchial management options may help to relieve some of their symptoms, allowing them freedom from shortness of breath as they go home, in conjunction with hospice or other palliative therapies.

One of the main advances in recent years in the field of smoking-induced chronic lung disease has been the identification of the syndrome of CPFE [14]. Not just a distinct phenotype of idiopathic pulmonary fibrosis (IPF), the syndrome of CPFE is characterised by the association of distinct features, including tobacco smoking, severe dyspnoea, unexpected subnormal spirometry, severely impaired transfer capacity for carbon monoxide, hypoxaemia at exercise, and characteristic imaging features (centrilobular and/or paraseptal emphysema, and diffuse interstitial opacities suggestive of pulmonary fibrosis of the lower lobes). The pathological features have not yet been formally studied. Pathophysiology of the syndrome beyond the obvious role of tobacco smoking remains to be explored [15]. Suspected in patients with dyspnoea and basal crackles unexplained by spirometry, the syndrome of CPFE can be recognised by the presence of both ''significant'' emphysema and fibrosis features on HRCT of the chest. Importantly, patients with the syndrome of CPFE have a high probability of severe pre-capillary pulmonary hypertension (PH) [14], which carries a poor prognosis, with only 60% survival at 1 yr from the date of right heart catheterisation [16]. Indeed, the risk of developing PH is notably higher in CPFE than in IPF without emphysema [17] and PH (and not only the presence of associated emphysema) represents the main independent determinant of mortality in patients with CPFE [14, 17].

There is strong evidence to support the relationship between tobacco smoking and interstitial lung damage. In this context, cigarette smoking has been associated as a causative agent in some diffuse parenchymal lung disorders, like desquamative interstitial pneumonia (DIP), respiratory bronchiolitis-associated interstitial lung disease (RBILD) and pulmonary Langerhans cell histiocytosis (PLCH), known as SR-ILDs [18]. This direct causative role for smoking in the pathogenesis of these disorders is based on significant epidemiological data, with a consistent preponderance of smokers within this population, the potential of disease remission upon smoking cessation, the existence of similar lesions, namely respiratory bronchiolitis, in healthy smokers without ILD, and the presence of a combination of these lesions in some affected smokers [19, 20]. Although these clinical cases, which occur primarily in relatively young adult smokers, are associated with characteristic and distinctive histopathological and radiological features, mixed patterns of SR-ILDs frequently coexist in the same patient, the most significant overlap being between RBILD and DIP, which provides evidence that RBILD, DIP and PLCH form a spectrum of interstitial patterns of lung injury related to cigarette smoke [21]. Recently, an outbreak of acute eosinophilic pneumonia (AEP) among US military personnel deployed in Iraq suggests that smoking may precipitate this acute entity in young adults with a recent onset of heavy tobacco use [22]. Thus, AEP may in some cases be considered a SR-ILD.

In conclusion, over the past 20 yrs the clinical perspective of smoking-related lung disease had expanded greatly. Clinicians are now aware of the many faces of the damage induced by cigarette smoking on the respiratory system. They have now better tools to recognise and distinguish them from other entities. Modern imaging techniques are surely part of this diagnostic armamentarium. Nonpharmacological treatments have been validated, such as pulmonary rehabilitation in COPD and emphysema and endobronchial stents in neoplastic airway obstruction, or have been proposed, such as endobronchial valves for some types of emphysema. In the future, we need more studies on the long-term effects of rehabilitation and physical activity in COPD and other smoking-related lung diseases, and new and simpler tools for the classification of SR-ILDs.

STATEMENT OF INTEREST

None declared.

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