Gastroesophageal Reflux in Idiopathic Pulmonary Fibrosis: More than a Gut Feeling?

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Idiopathic pulmonary fibrosis (IPF) is a destructive pulmonary disease, characterized by extensive scarring of the lung. This process leads to the loss of pulmonary function, progressive dyspnea, and finally death. For many years, IPF patients were treated with immunosuppressive agents based on the hypothesis that chronic inflammation was the pathobiological driver of disease. Such therapies have now been shown to be ineffective and possibly harmful: combination therapy with high-dose corticosteroids, azathioprine, and acetylcysteine had no impact on disease progression and resulted in higher morbidity and mortality than placebo [1]. Although two antifibrotic agents have now been developed that slow disease progression as measured by FVC decline [2, 3], the pathogenesis of this fibroproliferative disorder is still largely unknown despite intensive research in the last decades.

One of the central issues in the debate over disease pathogenesis at this moment is whether or not gastroesophageal reflux (through causing recurrent microaspiration of gastric contents) plays a role in the development and/or progression of IPF. This has become a particularly important issue as antiacid therapy has received a conditional recommendation for the treatment of IPF in the latest ATS/ERS/JRS/ALAT IPF practice guidelines [4]. Indeed, several retrospective studies have demonstrated an association between gastroesophageal reflux

(or the treatment of gastroesophageal reflux) and outcomes in IPF. Patients taking oral antiacid therapy appear to have a slower rate of decline in lung function [5] and improved survival [6]. In addition, there is evidence suggesting that gastroesophageal reflux may be an important cause of acute exacerbation [5, 7–8]. Both acid and non-acid reflux might play an important role, and in this respect, *Helicobacter pylori* could be an important factor [9].

In this issue of *Respiration*, Kreuter et al. [10] apply an interesting approach in order to shed more light on the relationship between gastroesophageal reflux, in particular nonacid reflux, and IPF. Their approach was original; they investigated whether *H. pylori*-containing microaspiration could be involved in IPF pathogenesis by performing PCR screening for *H. pylori* DNA in lung biopsy specimens of IPF patients. They were not able to demonstrate the presence of *H. pylori* DNA in lung biopsy tissue from IPF patients. In addition, the authors did not find a correlation between the use of corticosteroids and the presence of reflux (unfortunately, they did not investigate an effect of immunosuppressive agents such as azathioprine). In addition, they found that ex-smokers had less prevalent gastroesophageal reflux than current smokers.

While there are many potential explanations for the findings of Kreuter et al. [10] that have little to do with the relationship of gastroesophageal reflux-induced mi-

croaspiration and IPF (e.g. perhaps there was no microaspiration occurring at the time of biopsy, or there was no *H. pylori* in the microaspirate at the time of biopsy), it is worth using this interesting study as a cautionary chapter in the ongoing story of gastroesophageal reflux and IPF. The fact is that there remain no studies establishing a causal relationship between the two (association does not prove causation). It is equally plausible that gastroesophageal reflux more often occurs in fibrotic lungs as a result of fibrotic changes [11–12]. There are also no prospective, controlled trials of antireflux therapies, medical or surgical, from which we can draw conclusions about the effectiveness of antiacid therapies in IPF (although at least one trial is currently underway).

This should not discourage us from further investigation of the relationship between gastroesophageal reflux and IPF; the retrospective data are impressive. In addition, recent findings suggest that the airways might be involved at an early stage in IPF [13, 14], and the airway abnormalities seem not only to be related to zones of es-

tablished fibrosis, in contrast to what has been initially thought. This finding might be suggestive of a pathobiological role of gastroesophageal reflux, which would be hypothesized to initially affect the peribronchiolar regions more prominently.

We believe that the role of gastroesophageal reflux in the pathogenesis of IPF is still uncertain. In the light of the recent ATS guidelines that suggest gastroesophageal reflux therapy be considered for use in IPF, this message needs to be heard loud and clear. Kreuter et al. [10] should be commended for addressing this issue and for incorporating the nonacid component of reflux in their hypothesis. It is crucial that we prospectively study the impact of both acid and nonacid reflux in patients with IPF and test interventions such as proton pump inhibition (that treats primarily acid reflux) and gastric fundoplication (that treats both). It is only with solid clinical science that we can test whether our intuition – our ‘gut feeling’ – about gastroesophageal reflux and IPF is correct.

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