Published in final edited form as:

J Pathol. 2018 April ; 244(4): 383–385. doi:10.1002/path.5027.

From bad to worse: when lung cancer complicates idiopathic pulmonary fibrosis†

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Abstract

Patients with idiopathic pulmonary fibrosis have a significantly increased risk for the development of lung cancer. The morbidity and mortality of this disease combination are substantial, and, unfortunately, there are currently few data to help guide clinicians in its diagnosis and treatment. In a recent issue of this journal, Hwang *et al* presented one of the first studies to evaluate lung cancer in patients with idiopathic pulmonary fibrosis at the molecular level. They demonstrate variants in regulators of the cell cycle, which are known to be important in malignant transformation and may also be important in the pathogenesis of idiopathic pulmonary fibrosis. Further understanding of the pathogenic overlap between lung cancer and idiopathic pulmonary fibrosis could help point the direction to specific diagnostic modalities and targeted treatment of both conditions in the future.

Keywords

lung cancer; idiopathic pulmonary fibrosis; telomere; microRNA

We have often heard patients express relief when their surgical lung biopsies show the usual interstitial pneumonia pattern rather than lung cancer (LC). This relief, as is well known, is probably misguided. Idiopathic pulmonary fibrosis (IPF) is bad. The median survival of IPF patients is 3–4 years, and outcomes of IPF patients are often even poorer than those of patients with many types of cancer [1,2]. But there is worse. There are the very unfortunate few who develop both IPF and LC (IPF-LC). Independent of a diagnosis of IPF, LC remains the leading cause of cancer death in the USA, as well as the leading cause of cancer death in men worldwide [2,3]. The coexistence of IPF and LC cannot be coincidental. In fact, the prevalence of LC in IPF patients, which has been reported to be between 4.8 and 48% [4–7], is significantly higher than in the general population [2]. The cumulative incidence of LC

†Invited commentary for Hwang *et al.* Genomic profiles of lung cancer associated with idiopathic pulmonary fibrosis. *J Pathol* 2018; **244**: 25–35.

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Author contributions statement

SBS, JKA and DJK participated equally in the conception and writing of this commentary.

Conflict of interest statement: DJK has collaborative research funding from Regeneron Pharmaceuticals. SBS and JKA have no conflicts of interest to report. No primary human subjects or animal research is reported in this manuscript, and it is not subject to ethical oversight for research.

also increases dramatically each year after a diagnosis of IPF. One study reported cumulative incidence rates of 41% at 1 year and 82% at 3 years [7], and another reported cumulative incidence rates of 3.3%, 15.4% and 54.7% at 1, 5 and 10 years, respectively [6]. Although LC risk in IPF patients is associated with older age, a higher smoking index, and the presence of combined pulmonary fibrosis and emphysema, the association stands even after adjustment for these risk factors, suggesting that IPF itself is a substantial risk factor for LC [6,8,9].

How does the diagnosis of IPF go from 'bad to worse?' Or, more appropriately, what then can we say about the development of LC in patients with comorbid IPF? IPF-LC appears to have a unique phenotype – predominantly squamous cell cancer (unlike non-IPF LC, in which adenocarcinoma is most prevalent), frequently located in the periphery of the lower lobes adjacent to areas of fibrosis – sometimes termed 'scar-cinoma' [10]. What drives the unique phenotype of IPF-LC? IPF-LC may be the result of immune privilege – a metaplastic epithelium that evades immune surveillance because of a fibrotic microenvironment. Is the fibrotic stroma a rich source of signals to drive neoplasia? Clinically, the risk of LC in IPF patients presents the clinician with several conundrums. First, there are no current recommendations from expert panels to guide screening for LC in IPF patients. In general, routine imaging of IPF is not recommended [1]. Second, if LC is detected early in an IPF patient, can we actually do something about it? One recent study found that the overall survival among IPF-LC patients was 38.7 months, as compared with 63.9 months for patients with IPF alone [7], which may suggest that therapy for LC may have some negative impact. Additionally, among the patients who had IPF-LC, acute exacerbations were triggered by a medical procedure related to the diagnosis or treatment of the LC [7]. This high rate of adverse outcomes is sure to leave both patients and physicians uncertain and anxious about the clinical decision-making process. Clearly, there is a need for more refined diagnostic and therapeutic approaches to this population.

It is in this context that we read the new study from Hwang *et al,* who present one of the first studies to address the unique phenotype of IPF-LC at a molecular level. Retrospectively, they performed targeted resequencing of genes that are frequently mutated in cancer, on tumours from 35 patients with IPF-LC. These patients had undergone surgical resection, and the authors compared their data with publically available clinical and genomic data from two prior studies conducted in non-small-cell LC patients without IPF [11]. As in non-IPF LC, *TP53* was the most frequently mutated gene in IPF-LC. *BRAF* mutations were found in 17% of IPF-LC patients, all of whom were non-pV600E, so they would not be amenable to targeted therapy with agents such as vemurafinib or dabrafenib. There was a preponderance of C > T somatic transitions in the IPF-LC patients, despite significant smoking histories, which are more commonly associated with C > A transversions [12]. Here, the authors suggest a possible association with the *APOBEC* family of DNA deaminases. One patient had a *SMAD4* variant, which is a downstream mediator of transforming growth factor-β signalling, which, in turn, is known to be important in the pathogenesis of IPF. Notably, a similar study of IPF-LC and non-IPF interstitial lung disease associated with LC [13] found that, of the 15 IPF-LC samples that they reviewed, 73% had a *TP53* mutation, one had a *SMAD4* mutation, and one had a *PTEN* mutation, but none had a *BRAF* mutation.

Given the unique phenotype of IPF-LC, is there some pathogenic overlap between IPF and IPF-LC? If so, further understanding of these shared features could help point the direction to specific diagnostic modalities and targeted treatment of both conditions in the future. The authors found a common polymorphism in TERT, which encodes the catalytic component of the telomerase holoenzyme, in 94% of the patients with IPF-LC. The functional significance of this variant is unclear, as it is common, especially in the Korean population (86%) [14] This polymorphism (rs2736100) has been previously associated with both IPF and LC, independently [15,16]. Telomeres play an essential role in both diseases. Activation of the telomerase enzyme is a hallmark of cancer, as it promotes cellular immortalization by allowing bypass of replication-induced senescence [17]. Furthermore, mutations in telomere-maintenance genes are the most common identifiable causes of sporadic and familial IPF [18,19], and short telomeres constitute a risk factor for IPF [20,21]. Patients with telomere-mediated disease also show an increased incidence of cancer [22], probably because of the genome instability caused by short telomeres. This study did not report any functional variants in telomerase, and did not assess the germline status of the other telomere-associated genes that are found to be frequently mutated in IPF (i.e. RTEL1 and PARN). Further research on this subject is warranted, as patients with telomere-mediated disease are exquisitely sensitive to chemotherapeutics [23].

It is important to mention that the LCs in the Hwang et al study [11] were low-stage disease that occurred predominantly in the upper lobes away from areas of fibrosis in patients with relatively preserved lung function. This raises some concern that the samples analysed may not be completely generalizable to all IPF patients with LC, as IPF-LC tends to present in the lower lobes and to show the squamous cell carcinoma phenotype. Moreover, the pulmonary function of these patients suggests that only a very select population of patients may have been sampled here.

We applaud the authors for tackling this problem with a molecular approach. Many questions certainly remain for both researchers and clinicians. For the researcher, are these variants functional, and what is the cellular and molecular progression of IPF to IPF-LC? Will the findings from Hwang *et al* be generalizable to other populations with distinct genetic backgrounds? Are there molecular pathways activated uniquely in IPF-LC that could potentially be targeted? As we have noted above, there are no data on other telomerase complex gene variants, such as *RTEL1* and *PARN*. Furthermore, the role of *MUC5B* is increasingly being recognized as critical to the pathogenesis of IPF. For future studies, we would advocate deeper sequencing approaches. Sequencing should be accompanied by functional studies to determine the functionality of these variants. For the clinician, there are no recommendations for screening or for treatment. Although IPF-LC represents only a fraction of the IPF population, it is a dreaded complication. It exemplifies the transition from bad to worse. We hope that this study will serve as a foundation to renew interest in what IPF-LC can teach us about both LC and IPF.

Acknowledgements

This work was supported by NIH grant K99-R00 HL113105 to JKA and R01 HL126990 to DJK.

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