Editorial

The role of liquid biopsy in early diagnosis of Lung Cancer in patients with Pulmonary Fibrosis

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Key words:
- Pulmonary fibrosis
- Lung cancer
- Liquid biopsy

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Pulmonary fibrosis (PF) describes a condition in which the normal lung anatomy is replaced by a process of active remodeling, deposition of extracellular matrix and dramatic changes in the phenotype of both fibroblasts and alveolar epithelial cells, as a result of an abnormal wound healing process[1-8]. This condition can be idiopathic, as in idiopathic pulmonary fibrosis (IPF), or secondary to genetic disorders, lung parenchyma involvement in connective tissue disorders (CTDs), sarcoidosis[9] or to exposure to environmental toxins or radiation. IPF is the most common idiopathic form of pulmonary fibrosis that affects approximately 5 million people worldwide, leading to death more than 100.000 patients each year, the same as breast cancer[2]. IPF, as well as other forms of progressive fibrotic lung disease, present with a median survival of 3-5 years from the time of diagnosis, evidence that makes them the non-cancer lung diseases with the gravest prognosis[2,4-7].

Despite extensive research efforts pathogenesis of lung fibrosis remains elusive reflecting to a significant health burden and an unmet therapeutic need[10-12]. Recent FDA-approved anti-fibrotic compounds (pirfenidone and nintedanib) do not improve lung function and have shown minimal efficacy in affecting patients' survival[13-18]. In addition, none of these compounds has been tested prospectively in the context of IPF coexisting with major comorbidities[19] such as lung cancer[20]. Interestingly, it has been proposed that many of the hallmarks of aging and cancer including genomic instability, telomere attrition, epigenetic alterations, and mitochondrial dysfunction can be considered characteristic of the fibrotic lung[21].

Recent epidemiologic evidence suggests that 3 to 22% of patients with IPF develop lung cancer with a nearly 5-fold increased risk compared with the general population[22]. Lung cancer has a severe impact on PF patients' survival and quality of life. Despite abundant epidemiologic and mechanistic links between PF and lung cancer[23,24], there is considerable lack of knowledge on the diagnostic and therapeutic management of these patients. Current ATS/ERS/JRS/ALAT guidelines (2011) do not address this crucial issue[2].

The implementation of a minimally invasive diagnostic tool for the early identification and monitoring of patients with IPF and lung cancer development represents a major challenge. Liquid biopsies have been seminally developed for molecular profiling of tumors in a minimally invasive and less

time-consuming way. They are based on the principle that tumor cells and subsequently their DNA are released into the circulation and therefore circulating-free DNA (cfDNA) can be easily isolated and used for detection of mutations responsible for drug responsiveness or resistance. The first "liquid biopsies" were developed to detect circulating fetal DNA in blood of pregnant females in order to test for fetal aneuploidies, referred to as non-invasive prenatal testing (NIPT). These were rapidly evolved to frequently used tests capable of detecting trisomies with high specificity and sensitivity on mass scale. The development of liquid biopsies for applications in patients with cancer, though being more arduous, has recently received much of attention and currently being implemented as a novel diagnostic and prognostic tool.

The inability to perform molecular tumor profiling in almost 20% of patients with advanced stage lung cancer due to poor performance status, insufficient tissue and long turnaround time led to the implementation of the first PCR-based droplet-biopsy tests for BRAF (V600) and EGFR (T970M) mutations into clinical practice[25]. Similarly, almost half of patients with fibrotic lung disease become symptomatic when fibrosis has significantly progressed leading to severe functional impairment and thus are unfit to undergo surgical lung interventions. Moreover, surgical lung interventions in patients with pulmonary fibrosis have been strongly associated with disease acute exacerbations and increased peri- and post-operative mortality[26,27].

Despite the amenable need for non-invasive diagnostic procedures that will allow clinicians to predict lung cancer development in high risk populations including patients with fibrotic lung diseases, the application status of liquid biopsies in this setting has significantly lagged behind[28]. Our study group has spearheaded the field of molecular biomarkers that mirror disease progression and reflect treatment response in patients with IPF. We were the first group that implicated the role of circulating mitochondrial DNA as a biomarker of disease progression in patients with IPF[29]. Moreover, we have recently conducted the largest, so far, biomarker study in the field of lung fibrosis and identified a 52-gene signature that correlated with disease clinical outcomes in 6 different cohorts of patients with IPF[30]. Importantly, in a follow-up biomarker study, researchers identified an epithelial biomarker signature that was strongly correlated with disease mortality. Interestingly, among the most highly-enriched genes were CA-19-9 and CA-125 two cancer-related antigens that are commonly elevated in patients with specific types of cancer including pancreatic, ovarian and lung[31]. The application of similar prediction tools comprising a panel of analytes that reflect both pathologies, lung fibrosis and cancer, may revolutionize current problematic diagnostic modalities and allow clinicians to timely apply personalized medicine therapeutic approaches[32-34].

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