REVIEW

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Does Chronic Microaspiration Cause Idiopathic Pulmonary Fibrosis?

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ABSTRACT

Idiopathic pulmonary fibrosis is a diffuse fibrotic lung disease of unknown etiology with no effective treatment. Emerging data support a role for chronic microaspiration (ie, subclinical aspiration of small droplets) in the pathogenesis and natural history of idiopathic pulmonary fibrosis. However, the precise relationship between chronic microaspiration and idiopathic pulmonary fibrosis remains unknown. Gastroesophageal reflux, a presumed risk factor for microaspiration, has been strongly associated with idiopathic pulmonary fibrosis with an estimated prevalence of up to 90%. This review aims to describe the relationship between chronic microaspiration and idiopathic pulmonary fibrosis by laying out the clinical and biologic rationale for this relationship and exploring the scientific evidence available. The gaps in our current understanding of the diagnosis of chronic microaspiration and idiopathic pulmonary fibrosis and the ongoing uncertainties in management and treatment will be highlighted. Defining the role of chronic microaspiration in idiopathic pulmonary fibrosis is essential as it has potential clinical, pathobiological, and treatment implications for this deadly disease.

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Idiopathic pulmonary fibrosis, often abbreviated as IPF, is a chronic, fibrotic lung disease.[1] There is no proven therapy, and the median survival is between 2 and 3 years from the time of diagnosis.[2] By definition, the cause of idiopathic pulmonary fibrosis is unknown, although several associations have been described: cigarette smoking; exposure to wood and metal dusts; chronic viral infection; exposure to some drugs (eg, antidepressants); and hereditary factors (eg, mutations in the genes encoding telomerase components).[1,3,4]

Recent focus has shifted to the potential role of chronic silent microaspiration (ie, subclinical aspiration of small droplets) in the pathogenesis of idiopathic pulmonary fibrosis.[1] Further, it has been suggested that the acute respiratory

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Conflict of Interest: Dr. Lee has no conflicts of interest to disclose. Dr. Collard has provided consulting services to Actelion, Amira, InterMune, Gilead Science, Genzyme, CV Therapeutics, Nektar Therapeutics, and Roche, has served on an advisory committee for InterMune, and speaks regularly about idiopathic pulmonary fibrosis. Dr. Raghu has given lectures on the diagnosis and management of interstitial lung diseases and has discussed the potential role of chronic silent microaspiration in the pathogenesis of idiopathic pulmonary fibrosis. Dr. Sweet has no conflicts of interest to disclose. Dr. Hays has no conflicts of interest to disclose. Dr. Campos has no conflicts of interest to disclose. Dr. Golden has no conflicts of interest to disclose. Dr. King has given lectures on the diagnosis and management of interstitial lung diseases and has discussed the recent papers that have discussed the potential role of chronic silent microaspiration in the pathogenesis of idiopathic pulmonary fibrosis and as a potential cause of the acute respiratory decompensation manifested by some patients with idiopathic pulmonary fibrosis. In 2007, Dr. King provided expert testimony that a patient's diffuse parenchymal lung disease (lung fibrosis) was, more likely than not, caused by chronic aspiration.

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decompensation (ie, acute exacerbation) manifested by some patients with idiopathic pulmonary fibrosis may be due to microaspiration.[5] As a result, there is a growing consensus that elucidating the impact of microaspiration on the pathogenesis and natural history of idiopathic pulmonary fibrosis is important.

This review aims to explore the relationship between microaspiration and idiopathic pulmonary fibrosis, highlighting the scientific evidence supporting a potential causative role. Our hope is to raise awareness of this topic among clinicians and scientists, establish a solid foundation for future scientific investigation in this field, and emphasize the need for further studies to determine the significance of microaspiration in idiopathic pulmonary fibrosis.

CLINICAL SIGNIFICANCE

- Idiopathic pulmonary fibrosis (IPF) is a progressive and frequently fatal fibrotic lung disease of unknown cause.
- Chronic aspiration has been shown to cause pulmonary fibrosis in animal models.
- There is a strong association between abnormal gastroesophageal reflux, a presumed risk factor for microaspiration, and IPF.
- If microaspiration is important to the pathogenesis of IPF, prevention of microaspiration might improve outcomes.

SILENT MICROASPIRATION AND LUNG DISEASE

Aspiration is defined as the inhalation of oropharyngeal or gastric contents into the larynx and lower respiratory tract.[6] The clinical syndrome due to aspiration (eg, aspiration pneumonitis, aspiration pneumonia) depends on the nature and volume of aspirated material, the frequency of aspiration, and the host's response to the aspirated material.

The term "silent" microaspiration is used when patients have asymptomatic aspiration of small volumes of oropharyngeal secretions or gastric fluid into their lungs. Approximately half of all healthy adults aspirate small amounts of oropharyngeal secretions during sleep,[7] and other comorbidities may increase the risk of aspiration (eg, scleroderma, cerebrovascular disease, and degenerative neurologic disease).[6,8,9] However, normal host defenses (eg, glottis closure, cough reflex) are usually able to compensate.[10] Depending on the frequency and intensity of the silent microaspiration and, perhaps, genetic predisposition, patients might manifest with cough, wheeze, or mild gas exchange abnormalities.[11]

Gastroesophageal reflux and silent microaspiration is associated with several lung diseases and is common among those who have had lung transplantation.[12,13] Lipoid pneumonia is caused by the silent microaspiration of exogenous lipid (usually a complication of long-term ingestion of oil-based compounds) that leads to a chronic inflammatory pneumonitis that often progresses to fibrosis.[10] Silent microaspiration also has been suggested as a cause of chronic bronchiolar and interstitial lung disease.[14] Lastly, data from the lung transplantation literature strongly suggest that chronic silent microaspiration is associated with post-transplantation bronchiolitis obliterans, the primary lesion in chronic organ rejection.[15] In fact, several studies have suggested that early fundoplication improves survival and decreases chronic allograft rejection in this population, presumably through reducing the frequency of silent microaspiration.[16,17]

SILENT MICROASPIRATION AND PULMONARY FIBROSIS

Evidence from experimental models in animals and descriptive studies in humans support the concept of microaspiration as a potential cause of pulmonary fibrosis.

Animal Data

Acute Aspiration. Gastric juice is found to have rapid distribution in the lungs and is detected in the subpleural zones within 20 seconds following instillation in the main bronchus of dogs.[18] Delivery of a single dose of acid solution to the lungs of rabbits and dogs leads to a wide array of histopathologic changes, including alveolar hemorrhage, pulmonary edema, and neutrophilic inflammation.[19,20] A low-mortality acid aspiration lung injury model demonstrated loss of normal parenchymal architecture and widespread collagen deposition at 2 weeks.[21] In addition, acid-treated rodent lungs have demonstrated increased transforming growth factor (TGF)-beta 1 expression in the lung lavage and increased expression of collagens III/IV and fibronectin in the lung tissue, suggesting profibrotic mechanisms might be involved in aspiration-induced lung fibrosis.[22]

Chronic Aspiration. Histologic specimens from rodent models of repetitive gastric fluid aspiration exhibited prominent giant cells, lymphocytic and obliterative bronchiolitis, and parenchymal fibrosis.[23] Cytokine analysis showed increased production of TGF-beta. The effects of whole gastric fluid as well as its individual components also were studied using a similar chronic aspiration model.[24] Interestingly, their findings, characterized by granulomatous interstitial pneumonitis, were independent of gastric fluid pH.

Human Data

In Vitro Studies. There are limited in vitro data on the effects of gastric fluid aspiration on human epithelial cells, alveolar macrophages, and resident fibroblasts. A component of bile acid, chenodeoxycholic acid, has been shown to induce TGF-beta production from human airway epithelial cells via a p38 MAP-kinase dependent pathway.[25] Fibroblast cell proliferation also was increased with exposure to chenodeoxycholic acid, a response that was inhibited by dexamethasone and anti-TGF-beta antibodies.