

mitochondria by cellular clean-up mechanisms known as mitophagy [13-15]. PINK1 has been extensively studied in the neuronal system as inherited mutations of PINK1 are associated with an early onset of Parkinson's Disease (PD) [16]. Models of PINK1 deficiency in *Drosophila*, zebrafish, and *in vitro* silencing of PINK1 result in impaired electron transport chain function, altered mitochondrial fission-fusion dynamics, increased oxidative stress, and changes in mitophagy, leading to cellular apoptosis. Interestingly, mice deficient in PINK1 show dysfunctional mitochondria in the heart and cerebral cortex with age or after exposure to cell stress, suggesting PINK1 has an important function as a regulator of mitochondrial stress responses [17, 18]. Thus, although PINK1 is ubiquitously expressed [19], PINK1 mutations can affect mitochondrial quality control differently according to cell type, age, and levels of cell stress [17]. PINK1 is highly expressed in epithelial and neural tissues but lower in tissues of mesenchymal origin with the exception of muscle [20]. In the lung, up-regulation of PINK1 has been found in lung epithelia of chronic obstructive pulmonary disease patients [21]. We have found that AECII, but not fibroblasts, from IPF lung are deficient in PINK1 expression, and this loss of PINK1 is associated with accumulation of dysmorphic and dysfunctional mitochondria and these cells elaborate many profibrotic factors [22].

Our discovery between mitochondrial dysfunction and induction of fibrosis suggests that therapeutic opportunities to improve mitochondrial function might have a beneficial effect in the prevention or therapy of lung fibrosis. Mitochondrial antioxidants have been developed, including Mito Q, and have shown improvement of respiratory function in mitochondria [26-28]. Metabolic substrates of the TCA cycle are under study as therapeutic candidates against cancer and pulmonary hypertension [29-31].

In summary, our studies indicated that aging and ER stress have important effects on the physiology of AECII mitochondria and influence susceptibility to lung fibrosis. We showed that aging and ER stress were associated with deficient expression of PINK1 in alveolar type II epithelial cells. As has been observed in neurons, PINK1 can regulate mitochondrial homeostasis in the alveolar epithelial cells, and its reduction can lead to the accumulation of enlarged and damaged mitochondria, loss of cell viability, and activation of profibrotic responses. These data suggest that therapeutic pathways based on induction of PINK1 and/or improvement of mitochondrial function, dynamics, and turnover might be useful in the treatment of lung fibrotic diseases.

*For a list of references to this article, other articles in this issue, and the Division of PACCM's recent publications and suggested readings for this issue, visit [UPMCPHysicianResources.com/Pulmonology](http://UPMCPHysicianResources.com/Pulmonology).*

## Case Presentation: Lymphocytic Interstitial Pneumonia



**Eric Nolley, MD**

John is a 64-year-old retired chemist with a history of IgG4-related pancreatitis who presented to the Simmons Center with a subacute onset of dyspnea on exertion, cough, and an abnormal chest CT scan. He was diagnosed with IgG4 disease in 2011, when he experienced weight loss, parotid enlargement, and pancreatitis. He was treated with prednisone, experienced no more episodes of pancreatitis, and was transitioned to mycophenolate for maintenance immunosuppression. At that time, a serologic workup was negative including ANA, ANCA, anti-SSA, and anti-SSB among others. He also never had elevated peripheral levels of IgG4.

He was referred to the Simmons Center in 2015 for evaluation of IgG4-related lung disease. His pulmonary symptoms were relatively mild with only mild dyspnea on exertion and a chronic



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cough occasionally productive of clear sputum. We completed pulmonary function testing that revealed a mild obstructive ventilatory defect. His CT chest scan (Figure 1) showed clusters of nodules in an interstitial pattern that had progressed compared with prior studies in 2012 and 2014. We discussed his case at the Simmons Center multidisciplinary case conference, which consists of pulmonologists and experts in rheumatology, radiology, and pathology. We concluded that several features of his case were not consistent with IgG4-related pulmonary disease, including the absence of peripherally elevated IgG4 levels and atypical imaging characteristics. In consultation with our rheumatology colleagues, we were concerned for seronegative Sjögren's disease, which can also present with parotid swelling and pancreatitis. We were also concerned about atypical infection in

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the setting of his immunosuppression. Because of these concerns and because the nodules on his CT chest were progressing, we decided to evaluate further with a bronchoscopy.

We performed a bronchoscopy with bronchoalveolar lavage. All culture data were negative for infection. We performed transbronchial biopsies in order to obtain tissue to stain for IgG4 and evaluate for other etiologies, such as sarcoidosis or interstitial lung disease related to Sjögren's disease-lymphocytic interstitial pneumonia. The pathology showed small and large airways with a prominent lymphoplasmacytic infiltrate of polyclonal plasma cells with similarly appearing mononuclear infiltrates in a perivascular distribution and no granulomas (Figure 2). IgG and IgG4 immunostains were negative. Overall, these findings are most consistent with lymphocytic interstitial pneumonia (LIP).

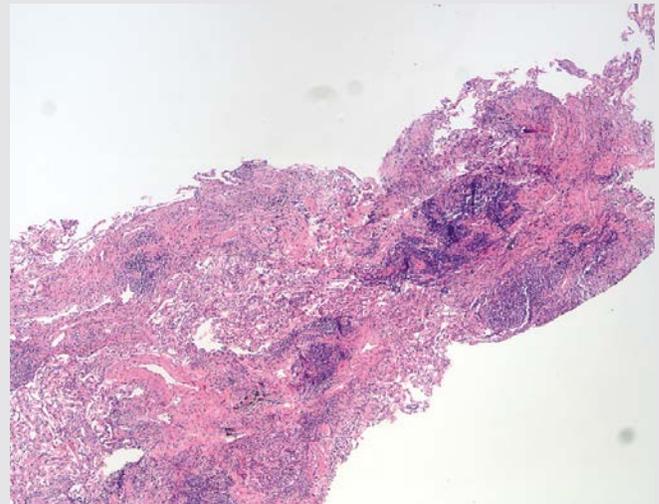
LIP is a benign lymphoproliferative disorder that presents with diffuse or focal lung involvement due to polyclonal proliferation of mature T- or B-cells. Most commonly associated with rheumatologic disease, one-fourth of all LIP cases are due to Sjögren's disease, which is the most likely diagnosis in this case. IgG4-related disease and Sjögren's disease likely exist on a spectrum and share similar organ involvement including salivary glands, gastrointestinal, pulmonary, and renal. However, given his normal

peripheral IgG4 levels and lack of IgG4 staining on transbronchial biopsy, John's lung disease is most consistent with seronegative Sjögren's-associated LIP. LIP is typically treated with steroids and potentially other immunosuppressive agents in the setting of declining lung function. Outcomes overall are good, with most patients experiencing resolution or stabilization often without treatment. There is a small risk of progression to pulmonary lymphoma and so patients require close monitoring to document the stability of the disease.

John's case exemplifies how the Simmons Center for Interstitial Lung Disease is well-positioned to diagnose and manage complex and rare pulmonary cases. Because of our multidisciplinary approach, we were able to consider and expertly evaluate for this rare interstitial lung disease. John's current management likely does not need to be changed because he has minimal symptoms on mycophenolate. However, he will require close monitoring of his CT scan to evaluate for stability versus progression to pulmonary lymphoma. Should he experience declining lung function or have progression of findings on his CT chest scan, we would work closely with our rheumatology colleagues to initiate treatment with rituximab.



**Figure 1.** CT chest scan demonstrating clusters of interstitial nodules that had progressed when compared to prior studies.



**Figure 2.** Transbronchial biopsy demonstrating lymphoplasmacytic infiltrate in a perivascular distribution.