In this issue of Respiratory Reader, we are privileged to provide updates from the Dorothy P. and Richard P. Simmons Center for Interstitial Lung Disease (ILD) at UPMC.

The Simmons Center was generously endowed in 2001 by the Simmons family with a charge to find the cause and the cure for idiopathic pulmonary fibrosis (IPF), and to care for patients and their caregivers. Over the past 15 years, the Center has seen more than 4,000 ILD patients from all over the United States. Due to the generous spirit of our patients who have enrolled in research studies, and our visionary leadership including former Director, Naftali Kaminski, MD, Medical Director, Kevin Gibson, MD, and clinical nurse specialist, Kathleen Lindell, PhD, RN, we have achieved international recognition for seminal discoveries in IPF. Samples from the Simmons Center have led to the discovery of the MUC5B and TOLLIP genes that are very highly associated with the development of IPF. We also have identified several proteins and genes, sampled from simple blood testing, to predict prognosis of IPF. We were privileged to serve as one of the centers for the clinical trials that tested the new FDA-approved therapies for IPF. In collaboration with Steven Duncan, MD, at the University of Alabama, Michael Donahoe, MD, has shown for the first time that the dreaded ‘IPF exacerbation,’ a frequently fatal complication of IPF, can be treated with therapies that target autoimmunity.

In April 2015, Daniel Kass, MD, assumed leadership of the Simmons Center in April 2015 and his laboratory explores the pathogenesis of IPF at its most basic levels to help devise new therapies for IPF and for all ILDs. Through his work alongside Dr. Gibson, Luis Ortiz, MD, and Kristen Veraldi, MD, PhD, referrals to the Simmons Center continue to grow. Additionally, Jared Chiarchiaro, MD, and Lauren Tomsic, RPA-C, have joined the Simmons Center team.

This issue includes highlights from the laboratory of Mauricio Rojas, MD, who has spearheaded studies of bone marrow-derived mesenchymal stem cells as therapies for respiratory failure and IPF; new data on the role of mitochondrial dysfunction in alveolar epithelial cells in IPF from Ana Mora, MD; and the critical importance of palliative care for patients with IPF from Dr. Lindell.

We hope you enjoy this issue of Respiratory Reader and we extend our best wishes for 2017.
Idiopathic pulmonary fibrosis (IPF) is a fatal lung disease characterized by progressive scarring of the lung [1, 2]. IPF prevalence dramatically increases with age, and aging is a known risk factor for IPF [3]. While familial pulmonary fibrosis has been associated with mutations in telomerase-related and surfactant proteins, the cause of the majority of sporadic IPF cases and the mechanisms involved in the aging susceptibility to IPF are unknown [4, 5]. One of the most compelling theories in IPF is the vulnerability of type II alveolar epithelial cells (AECII) to injury. This injury is associated with the presence of markers of cellular stress responses, secretion of pro-fibrotic cytokines, and increased apoptosis [6]. AECII are critical to regeneration of the injured lung. To repair the lung, AECII have high-energy demands and to accomplish this task, mitochondria accumulate in AECII, comprising approximately 50 percent of the lung mitochondrial mass [7, 8]. These observations suggested that mitochondrial dysfunction may be related to the pathogenesis of pulmonary fibrosis. We have found that the mitochondria in the AECII of IPF patients have an impaired capacity to repair the lung. The focus of our laboratory is to understand mitochondrial biology at the molecular level as a potential link between aging and the development of pulmonary fibrosis. We hope to uncover novel therapeutic targets to reverse mitochondrial pathology and ultimately IPF.

Mitochondria are the primary energy-generating organelles in most eukaryotic cells. While AECII are active progenitor and secretory cells with high-energy demands and high mitochondrial content, there is limited knowledge of the impact of aging on mitochondrial function or the role of mitochondria on the susceptibility to lung disease. Aging seems to affect mitochondria in particular. Abnormalities in mitochondria are often observed with aging, including enlargement and loss of the membrane structures known as cristae [9, 10]. Moreover, ATP production and respiration in mitochondria from aged animals are less efficient compared to mitochondria from younger animals, and often, aging mitochondria produce increased amounts of potential injurious reactive oxygen species (ROS) [11].

In our laboratory, we have found that age affects mitochondria in AECII and leads to impaired respiration [12]. In addition, we discovered that AECII from patients with IPF are characterized by the accumulation of dysmorphic and dysfunctional mitochondria. These mitochondrial changes are also associated with increased expression of markers of endoplasmic reticulum (ER) stress-inducing (Figure 1). These findings were recapitulated in aging mice in response to ER stress-inducing stimuli. We found that dysfunctional mitochondria in AECII from IPF and aging lungs were related to low expression of the regulator of mitochondrial homeostasis, Phosphatase and Tensin Homolog induced putative kinase 1 (PINK1), a kinase linked to age-related neurodegenerative disease. We recently discovered that young PINK1-deficient mice exhibited elevated susceptibility to apoptosis and spontaneous TGF-β-driven lung fibrosis, developing similar dysmorphic and dysfunctional mitochondria in AECII [12].

PINK1 plays a crucial role in the maintenance of mitochondrial morphology, function, and selective degradation of damaged
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.

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Case Presentation: Lymphocytic Interstitial Pneumonia

(continued from page 4)

definition 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.
Meet the Rojas Lab

Mauricio Rojas, MD

Mauricio Rojas, MD, is Associate Professor of Medicine and Scientific Director of the Simmons Center. Dr. Rojas and his wife Ana (see her article on the role of mitochondria in IPF on page three) joined the University of Pittsburgh in 2010. Their daughter Paula, an alumna of Pitt, will attend law school in the fall. Since 2004, the research in Dr. Rojas’ lab has focused on the use of bone marrow-derived mesenchymal stem cells, or MSCs, as an alternative therapy for lung repair after acute and chronic injury. His seminal observations using MSCs in animal models derived into clinical trials using MSCs in acute lung injury.

In collaboration with Jonathan D’Cunha, Chief of Lung Transplantation/Lung Failure at UPMC, Dr. Rojas created the Center for Advanced Organ Perfusion, in which donated lungs are perfused and ventilated for several hours to improve lung quality using different approaches, including MSCs, with the purpose of increasing the number of lungs that are suitable for transplant. This model has also been used by Dr. Rojas to complete preclinical studies of new drug candidates developed in our division.

Recently, his lab has concentrated on aging, and more particularly, on the consequences of aging in the lung. Because age is a major risk factor for many lung diseases, Dr. Rojas’ research is now focused on understanding how aging contributes to the pathogenesis of advanced lung disease such as IPF.

Members of the Rojas lab come from all over the world. They are dedicated to the mission of the Simmons Center and are passionately driven to perform cutting-edge research to translate bench research into the clinic to find a cure IPF. The quality of their work has been recently recognized by multiple awards in local and international conferences.

Human lungs are perfused, ex vivo

Cultured human bone marrow derived mesenchymal stem cells

Rojas Lab Team Members
Case Presentation: Hard Metal Pneumoconiosis

Hannah Otepka, MD

Edward is a 60-year-old man with a past medical history of hypertension who presented to the Simmons Center for Interstitial Lung Disease with dyspnea that began one and a half years prior. Working in construction, and amongst several exposures, he reports a history of welding tungsten more than 30 years ago. Edward first noticed dyspnea on exertion while painting with a silica-based compound. The dyspnea on exertion progressed over the course of a year, and at the time of referral, he reported shortness of breath at rest as well. He also described a dry cough, fatigue, and lightheadedness. Edward was first seen by a community pulmonologist who did a cardiac work-up which was negative. Edward then underwent computed tomography of the chest, which revealed bilateral upper lobe ground glass opacities and mild volume loss in the left upper lobe, without evidence of fibrosis. He was empirically started on a low dose of prednisone with great improvement in his symptoms. On the oral steroid, he was able to continue to perform his job doing manual labor.

Upon referral to the Simmons Center, his physical exam revealed stable vital signs and clear breath sounds; however, clubbing of his fingers was noted. Further pulmonary testing was completed as part of his initial visit. Pulmonary function tests resulted in a moderate restrictive ventilatory defect and low diffusing capacity. A serologic screen for autoimmune disease was unremarkable. Because the diagnosis still remained unclear, he underwent transbronchial biopsies of his left upper lobe. The lung biopsies were reviewed by Samuel Yousem, MD, Director of the Division of Anatomic Pathology at UPMC. He found abundant airspace giant cells, as well as macrophages with “cellular cannibalism” (Figure 1). In the setting of Edward’s remote exposure to tungsten, his improvement in symptoms with steroids, and his classic histopathology findings, he was diagnosed with hard metal pneumoconiosis, otherwise known as giant cell pneumonitis.

“Hard metal” is a synthetic compound made up of sintering tungsten carbide and cobalt, distinguishing it from other heavy metals [1]. When the lung is exposed to dust particles from these metals, hard metal lung disease (HMLD) may occur. HMLD presents as bronchitis, obstructive bronchiolitis, hypersensitivity pneumonitis, or fibrotic lung disease, otherwise known as hard metal pneumoconiosis [2]. Clinically, work-related subacute disease may occur, even at low levels of exposure, and eventually progress to interstitial lung disease. Radiographically, upper lobe ground glass opacities, reticular nodules, and traction bronchiectasis are most common, although in some cases, honeycombing fibrosis has been reported. For a definitive diagnosis, lung tissue must be obtained. The metals are soluble, and so they are not commonly seen on histopathology. However, alveolar macrophages and giant cells are commonly seen. As in Edward’s case, the finding of smaller inflammatory cells within the giant cells, otherwise known as cellular cannibalism, is classic and can help distinguish hard metal pneumoconiosis from other occupational lung diseases and hypersensitivity pneumonitis [3].

With limited data in the literature to support directed therapy for giant cell pneumonitis, Edward was presented at the Simmons Center multidisciplinary team conference. Patients are typically dependent on chronic therapy with corticosteroids. There is only anecdotal evidence to support the use of disease-modifying agents such as azathioprine or mycophenolate mofetil. After discussion about Edward’s case, the decision was made to begin him on mycophenolate, a steroid-sparing immunosuppressant agent, in the near future. Currently, he remains on a moderate dose of prednisone with most of his symptoms abated. He was counseled to avoid occupational exposures and to wear a respirator mask for lung protection if he continues to work in the exposed environment.

Diseases such as hard metal pneumoconiosis/giant cell pneumonitis are rare. Only case reports are available in the literature, and therefore diagnosis and treatment options can be challenging. Multidisciplinary academic centers such as the Simmons Center allows expert physicians in the field to serve patients like Edward and provide paramount clinical services, as well as efficient coordination of care.

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.
It Takes a Village: Multidisciplinary Discussion for Interstitial Lung Disease

Daniel J. Kass, MD

Jared Chiarchiaro, MD, MS

The diagnosis and management of interstitial lung disease (ILD) is one of the most challenging areas of pulmonary medicine. For many patients with ILD, it is difficult to assign a true diagnosis. When ILD patients deteriorate, as they frequently do, it is difficult to know whether to take an aggressive or conservative approach to therapy. These decisions are so complex that they often cannot be made in the office with the patient but require a conference with colleagues who bring a combination of experience and expertise to the table. At the Simmons Center, we provide a multidisciplinary approach to the diagnosis and treatment of ILD. Recent data suggest that multidisciplinary conferences can improve the diagnostic confidence of idiopathic pulmonary fibrosis (IPF) compared to diagnoses rendered by clinicians alone.

ILD is sometimes due to an underlying connective tissue disease, thus members of the Division of Rheumatology are key members of this conference. Robert Lafyatis, MD, Robyn Domsic, MD, and Thomas Medsger, MD, lead the UPMC Scleroderma Center. Chester Oddis, MD, and Rohit Aggarwal, MD, specialize in ILD associated with myositis. Ghaith Noaiseh, MD, has a special interest in ILD associated with Sjögren’s syndrome. These expert clinicians are also scholars who extensively publish on the role of autoimmunity in ILD. As pulmonologists, we often see patients with ILD in combination with our rheumatology colleagues and we work together to find the best medication to treat the underlying disease.

When the clinical and radiographic impression is most consistent with a diagnosis of idiopathic pulmonary fibrosis, patients often do not require a surgical lung biopsy. Thus, involvement of expert chest radiologists is a critical component in assigning a diagnosis to patients with ILD, in particular whether or not a patient has IPF. Diane Strollo, MD, and Carl Fuhrman, MD, are experts in chest radiology and frequently interpret the complicated chest imaging of our patients.

Histopathologic information has been shown to have the greatest impact on the final diagnosis, especially when the initial clinical and radiographic diagnosis is not consistent with idiopathic pulmonary fibrosis. Samuel Yousem, MD, E. Leon Barnes Professor of Anatomic Pathology and Vice Chairman of Anatomic Pathology Services at UPMC, interprets the pathology of ILD from within the UPMC system and provides consultations on ILD histopathology from both national and international providers. He is joined by Humberto Trejo-Bittar, MD, who trained at UPMC under the mentorship of Dr. Yousem in Thoracic Pathology.

Our multidisciplinary conference is also a critical part of medical education. Based on the multidisciplinary spirit of this conference, we have developed a medical student elective in ILD where students meet with the multidisciplinary faculty to learn about ILD through the eyes of pulmonologists, rheumatologists, radiologists, and pathologists. Moreover, our trainees challenge us with their questions, which forces us to remain current with the literature. This conference is loved by fellows and residents alike.

The questions that face our meeting are complex: For example, what is the diagnosis when a patient exhibits some signs of autoimmunity but fail to meet full diagnostic criteria for an autoimmune disease? How should they be treated? Does a patient have IPF, and should this patient be included in a clinical trial? Should the patient undergo a biopsy when there are potentially serious adverse consequences to surgery? What is the role of gastroesophageal reflux disease (GERD) in the progression of ILD? Our discussions are informed by both experience of the multidisciplinary team and our extensive knowledge of the ILD literature.

It takes a village to care for the patient with ILD. Multidisciplinary discussions are critical to diagnosis and management of these very complex patients. We at the Simmons Center are privileged to work with an outstanding multidisciplinary team. Patients and referring providers should know that a referral means more than a single visit in the office. A visit to the Simmons Center means a thoughtful and multidisciplinary approach to the evaluation and care for patients with ILD.

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