Normalization of Lung Function Following Treatment of Secondary Usual Interstitial Pneumonia: A Case Report

Laurie A. Hohberger[1], Felicia Montero-Arias[2], Anja C. Roden[3] and Robert Vassallo[1]

[1]Department of Medicine, Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, USA. [2]Department of Medicine, Division of Pulmonology, Hospital Mexico, San Jose, Costa Rica. [3]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA.

ABSTRACT: Usual interstitial pneumonia (UIP) is the most common idiopathic interstitial pneumonia (IIP) and is associated with a poor prognosis and poor responsiveness to immunosuppressive therapy. We present a case of a woman with steroid-responsive biopsy-proven UIP with significant and sustained improvement in pulmonary function. A female in her 40s presented following a one-year history of progressive dyspnea, a 20 lb weight loss, and fatigue. Imaging of the chest with computed tomography (CT) showed bibasilar subpleural reticular opacities and minimal peripheral honeycombing. Comprehensive connective tissue disease (CTD) antibody testing was negative. Pulmonary function testing showed moderate impairment with reduction in forced vital capacity (FVC, 69% predicted), forced expiratory volume in one second (FEV_1 73% predicted), and diffusing capacity for carbon monoxide (DLCO, 52% predicted). Surgical lung biopsy showed UIP with prominent inflammatory infiltrates. Following treatment with prednisone and azathioprine, the patient's symptoms resolved, while objective pulmonary function testing showed normalization of lung function, which is sustained at >4 years of follow-up. Improvement in lung function following immunosuppressive therapy is distinctly uncommon in either idiopathic or secondary UIP. This report suggests that occasionally, patients with secondary UIP occurring in the context of otherwise undefinable autoimmune clinical syndromes may be responsive to immunosuppressive therapy.

KEYWORDS: usual interstitial pneumonia, pulmonary fibrosis, connective tissue disease, immunosuppression

CITATION: Hohberger et al. Normalization of Lung Function Following Treatment of Secondary Usual Interstitial Pneumonia: A Case Report. *Clinical Medicine Insights: Circulatory, Respiratory and Pulmonary Medicine* 2015:9 23–25 doi: 10.4137/CCRPM.S22878.

RECEIVED: December 12, 2014. **RESUBMITTED:** February 18, 2015. **ACCEPTED FOR PUBLICATION:** March 07, 2015.

ACADEMIC EDITOR: Hussein D. Foda, Editor in Chief

TYPE: Case Report

FUNDING: This study is supported by a Rheumatology Research Foundation Pilot Grant award to RV. The authors confirm that the funder had no influence over the study design, content of the article, or selection of this journal.

COMPETING INTERESTS: Authors disclose no potential conflicts of interest.

CORRESPONDENCE: Vassallo.robert@mayo.edu

COPYRIGHT: © the authors, publisher and licensee Libertas Academica Limited. This is an open-access article distributed under the terms of the Creative Commons CC-BY-NC 3.0 License.

Paper subject to independent expert blind peer review by minimum of two reviewers. All editorial decisions made by independent academic editor. Upon submission manuscript was subject to anti-plagiarism scanning. Prior to publication all authors have given signed confirmation of agreement to article publication and compliance with all applicable ethical and legal requirements, including the accuracy of author and contributor information, disclosure of competing interests and funding sources, compliance with ethical requirements relating to human and animal study participants, and compliance with any copyright requirements of third parties. This journal is a member of the Committee on Publication Ethics (COPE).

Published by Libertas Academica. Learn more about this journal.

Introduction

Usual interstitial pneumonia (UIP) is the most common of the idiopathic interstitial pneumonias (IIPs).[1] UIP can be idiopathic (idiopathic pulmonary fibrosis, IPF), may be secondary to certain inhalational exposures and medications, or occur in the context of connective tissue diseases (CTDs). The detection of UIP on lung biopsy is important: UIP is less responsive to immunosuppressive therapy and is associated with a poor prognosis and a median survival of three to five years following diagnosis.[1] We report a unique case of a relatively young woman with non-specific systemic symptoms, moderate impairment in lung function, and UIP on surgical lung biopsy that improved on immunosuppressive therapy.

Case Presentation

The patient, a female never-smoker in her 40s, presented for evaluation of a one-year history of progressive dyspnea, a 20-pound weight loss, chronic fatigue, arthralgia, and Raynaud's phenomenon. Prior evaluation had showed an anti-nuclear antibody (ANA) titer of 1:80 and an elevated anti-Sjögren's-syndrome-related antigen (SSA) antibody. The physical examination was remarkable only for Velcro-type bibasilar crackles. Computed tomography (CT) of the chest showed subpleural reticular opacities most prominent at the bases with minimal areas of early honeycombing (Fig. 1). Comprehensive autoimmune CTD antibody testing was negative (despite known previous ANA positivity). Pulmonary function testing showed proportional reduction in forced vital capacity (FVC), forced expiratory volume in one second (FEV_1; 69% and 73% predicted, respectively), and diffusing capacity for carbon monoxide (DLCO; 52% predicted) (Fig. 2). Clinical rheumatology evaluation did not identify a specific CTD. Given the unclear clinical picture, a surgical lung biopsy was performed: in consideration of the chest imaging findings (Fig. 1), wedge biopsies were obtained from the anterior aspect of the right upper lobe and the inferior aspects of the right middle and lower lobes. Surgical lung biopsy showed predominantly mature fibrosis, honeycomb changes with regional heterogeneity, and fibroblast foci consistent with UIP: in addition, there were prominent inflammatory lymphoid infiltrates, mostly involving areas of fibrosis (Fig. 3). In consideration of the patient's young age, the suspicion of an unclassifiable underlying CTD, and the prominence of lymphoid infiltrates on lung biopsy, a trial of immunosuppression

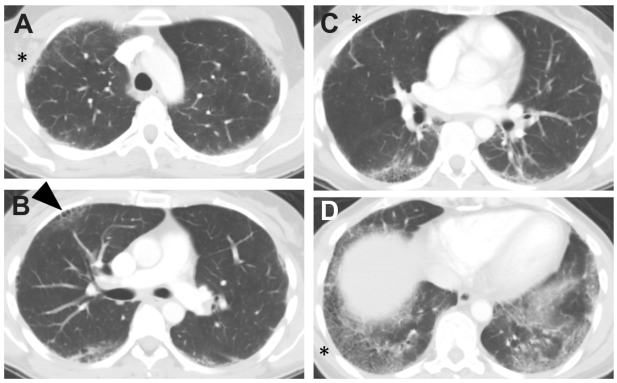

Figure 1. Representative chest tomographic (CT) images from the upper lobe (**A**), mid-lung region (**B**), and lower lobes (**C** and **D**) demonstrate bilateral, predominantly reticular, and peripheral opacities with associated traction bronchiectasis. The infiltrates are most prominent in the lung periphery and lower lung fields. Focal areas of early honeycombing may be seen in panel B (arrowhead).
Note: The sites marked by the asterisk (*) identify regions of the lung sampled at the time of surgical lung biopsy.

was initiated with prednisone 40 mg/day (0.5 mg/kg) for three months. At her three-month re-evaluation, she reported improved symptoms and significant improvement in spirometry (increase in FVC by 470 mL and FEV_1 by 570 mL) as well as DLCO (increase by 12%). Given the response to prednisone, she was initiated on azathioprine and titrated to a dose of 150 mg daily (2 mg/kg). Over the subsequent four years, the prednisone was tapered (dose reduced by 10 mg/day every month while on overlapping azathioprine therapy) and remission of symptoms was maintained with azathioprine. Longitudinal follow-up of lung function testing (performed every four to six months in the first two years after diagnosis and then annually) showed a progressive increase in FVC by

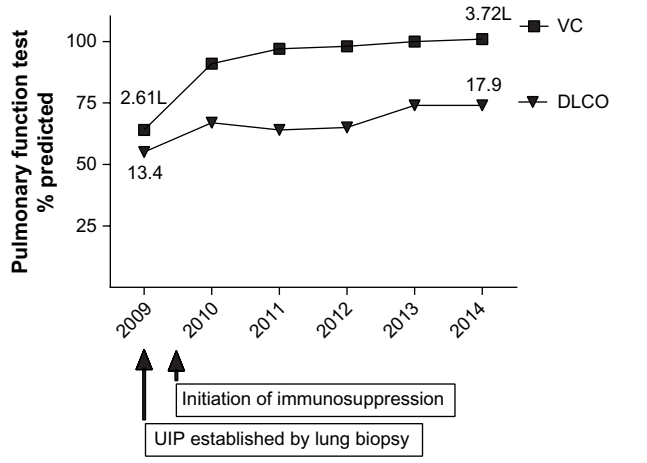

Figure 2. Graphical depiction of change in vital capacity (VC) and DLCO from the time of diagnosis to the final follow-up. The y-axis refers to the percent predicted pulmonary function variable (VC or DLCO) relative to age, gender, and height-matched peers. The absolute VC and DLCO values at diagnosis (2.61 L and 13.4) and as of last follow-up (3.72 L and 17.9) are shown in the graph.

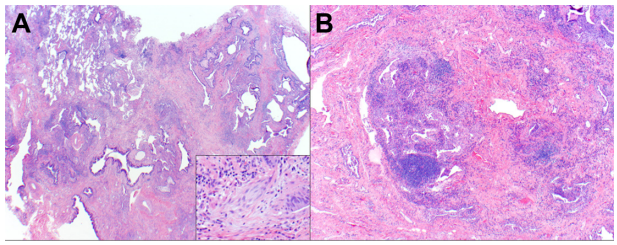

Figure 3. Surgical lung biopsy findings: (**A**) Low power view of the wedge biopsy from the right middle lobe lung shows mature fibrosis with honeycomb changes in the vicinity to alveolated lung parenchyma with preserved architecture and without fibrosis (regional heterogeneity). Within the mature fibrosis, there are fibroblastic foci (insert) (temporal heterogeneity) and areas of lymphoid infiltrate (**B**). These morphologic features are diagnostic of UIP. Magnifications ×20 (**A**), ×40 (**B**), and ×200 (**A**, insert).

a total of 1.1 L (31%). Her FEV_1 also improved by 860 mL (31%), and her DLCO by 4.5 (>20%) (Fig. 2). At the time of last follow-up in 2014, the patient was asymptomatic and her pulmonary function test was within normal limits. Nearly five years following initial presentation, the patient underwent full cardiopulmonary exercise testing with graded cycle ergometry and achieved a maximal workload of 175 W and a VO_2 max of 90% of that predicted for her age. At the level of highest workload, she breathed at 61% of the maximal voluntary ventilation (indicating normal ventilatory reserve) and recorded a normal ventilatory and gas exchange response throughout exercise. Chest X-ray performed at the most recent follow-up demonstrated normal lung volumes and mild interstitial prominence in the bases (Fig. 4).

Discussion

This unique case shows the unexpected clinical course of a patient with biopsy-proven UIP, occurring in the context of systemic symptoms that did not meet criteria for a definable CTD, in whom pulmonary function normalized on immunosuppression. There are several aspects of this case that merit reporting. The response of UIP to immunosuppressive therapy is distinctly uncommon, regardless of the underlying cause. Immunosuppression is not recommended in idiopathic UIP (IPF).[1] UIP is a pattern of lung injury that may be defined radiographically (presence of subpleural basal predominant reticular infiltrates, honeycombing, traction bronchiectasis, and minimal ground glass attenuation on high-resolution chest CT) or histopathologically (evidence of marked fibrosis with architectural distortion, honeycombing, fibroblastic foci, and temporal heterogeneity).[1] However, UIP is not synonymous with IPF; chronic hypersensitivity pneumonitis, CTD, drug toxicity, and asbestosis can all cause UIP.[1,2] Differentiating idiopathic UIP from the other causes of secondary UIP is of considerable importance clinically, and has therapeutic as well as prognostic implications.

Despite having a number of symptoms suggestive of an underlying CTD, our patient did not fulfill diagnostic criteria

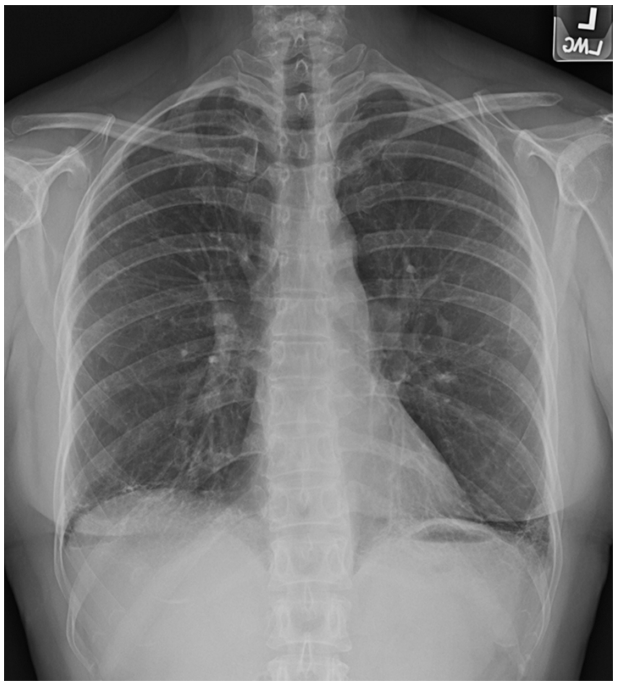

Figure 4. Chest radiograph, performed at the time of last follow-up, demonstrating preserved lung volumes and peripheral reticular densities in the mid-lungs and lower lung fields.

for any specific CTD, and to this date continues to have none of the symptoms consistent with any definable CTD. Such patients may be considered as having undifferentiated CTD or UCTD. These patients may pose a diagnostic dilemma in the multidisciplinary approach to management. In the absence of clinical features that would otherwise enable diagnosis of a definable CTD, there are often discrepant opinions regarding diagnosis and approach to therapy between rheumatologists and pulmonary specialists providing care for these patients. This is a category of patients also described as having *autoimmune-featured ILD* or *lung-dominant CTD*.[3–5] Interestingly, patients with autoimmune-featured ILD with UIP-pattern and positive autoantibodies were found to have more germinal centers and plasma cells on biopsy when compared to those with UIP and negative autoantibodies (as with our patient).[5] Prior reports identified the UIP-pattern on chest imaging and lung biopsy in most autoimmune-featured ILD.[5] A recent study by Kim et al also identified UIP as more prevalent than non-specific interstitial pneumonia (NSIP) in a cohort of 105 patients (42% vs 28%, respectively) with UCTD.[6] In that study, the three-year survival of UCTD-UIP was reported at 76.6%, and was significantly better than a matched cohort with IPF ($P = 0.042$).[6] Little is known about the natural history of disease in these patients, but unlike the patient reported herein, the survival reported in some series is relatively poor.[5] Patients with established CTD and secondary UIP are often treated with immunosuppressive therapies, despite limited evidence of efficacy. Stabilization of lung function may be encountered in some cases of CTD-associated fibrotic diffuse lung disease, but sustained improvement in lung function is distinctly uncommon. The current case does not provide rationale for the routine use of immunosuppressive therapy in biopsy-proven UIP. However, this case demonstrates the potential for certain types of secondary UIP occurring in the context of a non-definable systemic autoimmune illness, to respond to immunosuppressive therapy and be associated with a relatively good prognosis.

Conclusion

Improvement in lung function following immunosuppressive therapy is distinctly uncommon in either idiopathic or secondary UIP. This report does not provide justification for routine use of immunosuppression in the management of secondary UIP. However, it does suggest that, occasionally, the UIP lesion occurring in young persons with clinical features of an autoimmune disease, which might be otherwise unclassifiable, may be responsive to immunosuppressive therapy. The natural history and long-term prognosis for these patients remain to be established by prospective studies.

Consent

Publication of this report was discussed with the patient, and oral consent was provided by the patient to proceed with submission and publication. Mayo Clinic does not require IRB approval for publication of individual case reports.

Author Contributions

LAH and FMA analyzed and interpreted the patient data and drafted the manuscript together. ACR provided input and imaging for the histopathology and provided critical input regarding manuscript content. RV edited and prepared the final version of the manuscript and figures/tables. All authors read and approved the final manuscript.

REFERENCES

1. Raghu G, Collard HR, Egan JJ, et al; ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med*. 2011;183:788–824.
2. Fischer A, du Bois R. Interstitial lung disease in connective tissue disorders. *Lancet*. 2012;380:689–98.
3. Fischer A, West SG, Swigris JJ, Brown KK, du Bois RM. Connective tissue disease-associated interstitial lung disease: a call for clarification. *Chest*. 2010;138:251–6.
4. Tzelepis GE, Toya SP, Moutsopoulos HM. Occult connective tissue diseases mimicking idiopathic interstitial pneumonias. *Euro Res J*. 2008;31:11–20.
5. Vij R, Noth I, Strek ME. Autoimmune-featured interstitial lung disease: a distinct entity. *Chest*. 2011;140:1292–9.
6. Kim H-C, Ji W, Kim MY, et al. Interstitial pneumonia related to undifferentiated connective tissue disease: pathologic pattern and prognosis. *Chest*. 2015;147:165–72.