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# Organizing Pneumonia Secondary to Statin Use – A Dilemma

## **Cover Page Footnote**

To, The Editor Sub: Submission of Manuscript for publication Dear Sir, We intend to publish an article entitled “Organizing Pneumonia Secondary to Statin Use – A Dilemma” in your esteemed journal as a Case Report. This is an uncommon presentation of an uncommon disease and knowledge of this condition would aid in the appropriate diagnosis and management. On behalf of all the contributors I will act and guarantor and will correspond with the journal from this point onward. Prior publication - This article has not been previously published in another journal. It has been presented as a poster at TMA annual meeting at Murfreesboro, TN in Apr 2016. Support- There were no sources of funding Conflicts of interest - The authors do not have any conflicts of interest to declare. Permissions – There is no content included which is reproduced from any other journal. We hereby transfer, assign, or otherwise convey all copyright ownership, including any and all rights incidental thereto, exclusively to the journal, in the event that such work is published by the journal. Thanking you, Enambir Singh Josan, MD (Corresponding author) Resident Physician Department of Internal Medicine East Tennessee State University

Title of the article: Organizing Pneumonia Secondary to Statin Use.

Abstract:

A 70-year-old male with a medical history of chronic bronchitis, obstructive sleep apnea, atrial fibrillation, remote 40 pack year smoker but no occupational exposure presented with gradual onset of a dry cough, dyspnea on exertion and fatigue. His symptoms had been worsening over the course of 1 year. On physical exam, he was noted to have decreased breath sounds diffuse & bibasilar rales. CT chest showed extensive ground-glass opacities throughout the lower lobes, inferior half of right upper lobe and right middle lobe. A trial of antibiotics failed, and his pulmonary function test showed a restrictive pattern. Infectious, neoplastic and connective tissue disorders were ruled out systematically. Ultimately wedge resection with histology revealed evidence of organizing pneumonia. The patient was on simvastatin which was stopped. This, along with a course of corticosteroid led to clinical and radiological improvement.

Key-words:

Interstitial lung disease, organizing pneumonia, statin.

Key Messages:

Organizing pneumonia is a type of interstitial lung disease which mimics pneumonia in presentation but has an entirely different management. Statins have been implicated in pathogenesis with partial relapse after stopping therapy.

Introduction:

Interstitial lung disease (ILD) is a well-studied group of pulmonary disorders characterized by infiltration of lung interstitium at the expense of gas exchange. They are best classified by exposure (figure 1). The diagnosis of ILD is ever so complex due to similar radiologic and clinical characters with biopsy being the ultimate tool for differentiation.

Idiopathic interstitial pneumonia (IIP) is a type of ILD with no identifiable cause. It includes organizing pneumonia (OP) which is characterized by histological appearance of intra-alveolar organization with patchy consolidation. Here we describe an unusual case of OP associated with statin use.

Case History:

A 70-year-old male with medical history of chronic bronchitis, obstructive sleep apnea, atrial fibrillation, remote 40 pack year smoker but no occupational exposure presented with gradual onset of a dry cough, dyspnea on exertion and fatigue. His symptoms had been worsening over the course of 1 year. On physical exam, he was noted to have diffusely decreased breath sounds with bibasilar rales.

CT chest showed extensive ground-glass opacities (GGO) throughout the lower lobes (LL), inferior half of right upper lobe (RUL) extending into right middle lobe (RML) as shown in figure 2a. There was thickening of interlobular septae with relative sparing of anterior aspects. It also showed hilar lymphadenopathy and bilateral posterior pleural thickening. He failed a course of antibiotics and interval CT chest in 4 months showed worsening bilateral lung infiltrates. He also demonstrated restrictive pattern on pulmonary function testing which had worsened from two

years ago. Echocardiography showed ejection fraction of 50-55%, RVSP 45-50 mmHg. He was evaluated with bronchoscopy which showed hyperemic erythematous abnormal mucosa in RUL & left LL bronchus. Bronchial biopsy, washings, and lavage from RUL were negative for malignancy, fungal and acid-fast organisms. Endobronchial ultrasound was inconclusive alongside needle aspiration of right paratracheal and sub-carinal lymph nodes. Repeat imaging reported progression of extensive ground-glass, so lung biopsy was done which demonstrated evidence of organizing pneumonia (figure 3a) associated with scattered multinucleated giant cells. The surrounding lung showed alveoli with foamy macrophages, lymphoid hyperplasia (figure 3c), patchy cellular interstitial pneumonia with fibrosis (figure 3b, 3d) and evidence of smoking history in the form of respiratory bronchiolitis. These findings were not sufficient to warrant a diagnosis of 'Usual interstitial pneumonia' or 'Nonspecific interstitial pneumonia.' Prominent alveolar foam cells with lamellar inclusions raised the possibility of a drug reaction. Similar changes have also been described in patients on statin. Workup for connective tissue disease: ANA, Scl-70, Ro and La antibodies, Rheumatoid factor, fungal serologies and Immunoglobulin levels were unremarkable. HIV, Hepatitis panel, and Quantiferon TB gold were negative as well. Simvastatin was stopped, and he was started on prednisone which led to improvement in respiratory symptoms as well as partial resolution of GGO on follow up visit (figure 2b).

#### Discussion:

Organizing pneumonia (OP) derives its name from its clinical resemblance to early stages of pneumonia such as dyspnea, cough, fever and malaise and is characterized by histological intra-alveolar organization. It is classified as a sub-type of idiopathic interstitial pneumonia (IIP) as shown in figure 1. <sup>[1, 2]</sup> Although the primary pathology is at the level of alveoli, it is considered an IIP due to imaging and histological similarities. <sup>[3]</sup> OP can be secondary to infection, drug toxicity, connective tissue disease or can be cryptogenic when no cause is identified. <sup>[4]</sup> Both have similar clinical and imaging features, but Cryptogenic OP (COP) has better prognosis with rapid radiological and clinical response to corticosteroid therapy. <sup>[5]</sup>

It most commonly presents in a pattern of patchy consolidation with involvement of alveolar wall; nodular opacities involving the lumen of distal bronchioles, alveolar ducts, and walls. <sup>[4]</sup>

OP occurs because of protein leak into the alveolar lumen and eventually leading to an inflammatory injury and fibrin formation. The characteristic air space fibrosis is composed of fibroblasts arranged concentrically and extended into the interstitium. <sup>[6]</sup> COP (previously known as bronchiolitis obliterans organizing pneumonia) is unique in the aspect that no infective agent or cause is associated with it. <sup>[7, 8]</sup>

OP has an incidence of 1.97/100,000 in an Icelandic study (COP 1.1 and Secondary OP 0.87/100,000). <sup>[9]</sup> On the contrary side, the incidence of COP is 6-7/100,000 hospital admissions in a Canadian study. <sup>[10]</sup> Age distribution is most prominent in fifth to sixth decade with no variation with gender. It commonly presents with a gradual onset of dyspnea, dry cough, pleuritic chest pain, fever or malaise and extra-pulmonary signs of autoimmune diseases. <sup>[11]</sup> Acute respiratory failure at initial presentation is uncommon but should be considered when infectious and reactive airway diseases have been ruled out. The association of statin use (especially simvastatin) has been reported to be causative agent for OP and was characterized by diffuse cytoplasmic accumulation of intra-lysosomal lamellar inclusions. <sup>[12]</sup> The history and timing of exposure, the clinical and imaging evidence of disease as well as improvement after the discontinuation should be discussed. <sup>[13]</sup> We stopped the statin in our patient which led to partial resolution of symptoms along with

steroid regimen.

It may be necessary to rule out connective tissue disease with sero-markers and clinical correlation. Inflammatory markers such as Erythrocyte sedimentation rate and C - reactive protein may be elevated but are inherently non-specific. Patients diagnosed with Acute Myelogenous leukemia (particularly with chromosome 16 inversions) have been noted to have increased risk of pulmonary complications including COP. <sup>[14]</sup> Similar findings have also been reported in association with cytarabine use in leukemic patients. <sup>[15]</sup>

A plain radiograph is often non-contributory but 'High-resolution Computed Tomography' is very sensitive in detecting the consolidation, multiple ground glass opacities, and nodules which are most common at presentation and often in a sub-pleural or peri-bronchovascular distribution. <sup>[16]</sup> However, imaging can be non-specific with similar findings can be noted in some malignancies, drug reactions, and collagen vascular diseases. <sup>[11]</sup> Hilar and mediastinal lymphadenopathy is not a feature of COP, although rarely present and can side-track the diagnostic evaluation towards workup for malignancy as in the current case. <sup>[17]</sup> Reverse halo sign is noted to be very specific but is only present in about 20% cases. <sup>[18]</sup> Patients usually have mild restrictive pattern and impaired diffusion, but obstructive pattern can be seen in smoker. <sup>[4, 7]</sup>

Bronchoalveolar lavage (BAL) should be done in all patients to rule out infections and malignancy. A mixed pattern at differential cell count on BAL with few plasma cells and mast cells can help with diagnosis. <sup>[3]</sup> Video-assisted thoracoscopic surgery (VATS) is very effective for tissue diagnosis of ILD which is otherwise unclassified or undefined. However, the associated post-operative complications (includes infections, atelectasis & pneumothorax) can be as high as 65.6%. Even though the 30-day mortality was 0%, the 90-day mortality was close to 5% in a study. <sup>[19]</sup>

A way of quantifying the mortality risk is identification of patient at risk of death based on lymphatic distribution. The superficial lymphatic system is affected secondary to remodeling during the disease process which leads to impairment of alveolar clearance and causes delay in organ repair. <sup>[20]</sup> Minimal symptoms do not warrant therapy, and it may be beneficial to monitor without treatment. Steroids are very effective in most subjects and ensure complete recovery reported in about 60% subjects. <sup>[21]</sup> However, there is a high relapse rate once the treatment is stopped and re-establishment of therapy with increased dose is beneficial. <sup>[4, 7, 8, 22]</sup> Steroid-sparing therapy with cyclophosphamide is another option.

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Figure Legend:

Figure 1 – Classification of Interstitial lung disease.

Figure 2 – A: CT chest depicting extensive ground-glass opacities throughout the lower lobes, inferior half of right upper lobe extending into right middle lobe. B: Follow up chest imaging shows improvement in patchy ground glass opacities which were less extensive in comparison.

Figure 3 – Lung wedge biopsy with hematoxylin and eosin stain depicting: A- Organization with cellular interstitial infiltrate. B-Organizing pneumonia with some interstitial fibrosis. C-Lymphoid hyperplasia. D-Lymphoid hyperplasia with some interstitial fibrosis.