Respiratory Medicine Case Reports 31 (2020) 101283

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: http://www.elsevier.com/locate/rmcr

Case report

Complex obstructive lung disease – A diagnostic and management conundrum

Danielle R. Glick [a], Jeffrey R. Galvin [b], Janaki Deepak [a,c,*]

[a] Division of Pulmonary and Critical Care Medicine, University of Maryland School of Medicine, Baltimore, MD, USA
[b] Department of Diagnostic Radiology, University of Maryland School of Medicine, Baltimore, MD, USA
[c] Baltimore Veterans Affairs Medical Center, Baltimore, MD, USA

ARTICLE INFO

Keywords:
Rheumatoid arthritis
Obstructive lung diseases

ABSTRACT

Rheumatoid arthritis (RA) is a common autoimmune disease most well-known for its inflammatory, destructive polyarthropathy. Extraarticular manifestations of the disease may involve the respiratory system, including interstitial lung disease, pleural disease, pulmonary vascular abnormalities, and airways disease. Smoking is highly prevalent in the RA population, and may even have a synergistic effect in disease development and progression. In the diagnosis of pulmonary disease, this presents a unique diagnostic and therapeutic challenge. We present a case of a woman in her 50s who presented for evaluation of dyspnea and was found to have obstructive lung disease. In addition to RA, she had a significant smoking history and also owned pet birds, making definitive diagnosis difficult. Ultimately, chest imaging was crucial in identifying RA-related lung disease as the root cause of her symptoms, leading to successful treatment and symptom management.

1. Background

The pulmonary manifestations of rheumatoid arthritis (RA) are many and varied. Rheumatoid nodules are common, as is follicular bronchiolitis [1–3]. It can affect the large and small airways alike. In fact, the small airways can often manifest changes on imaging despite normal pulmonary function testing in asymptomatic non-smokers with RA [4]. In addition to the wide variation of presentations, it can often be difficult to diagnose RA-related lung disease due to the presence of competing diagnoses. Smoking is known to be associated with and possibly even causative of RA, and many population-based cohort studies have shown confounding of the incidence of obstructive lung disease from smoking [5,6]. However, some studies have shown increased incidence of obstructive pulmonary function testing in non-smoking RA patients [7]. In patients where there exist multiple exposures and potential etiologies for pulmonary disease, it can be difficult to isolate and treat a primary diagnosis [8] With the express consent of the patient, we present a case of complex obstructive lung disease with significant contribution of RA-related small airways disease, which created a diagnostic and therapeutic challenge.

2. Case presentation

A Caucasian woman in her late 50s with a known history of Rheumatoid Arthritis, celiac disease, diabetes mellitus type 1, childhood asthma, and a 70-pack-year smoking history presented to the pulmonary clinic for initial evaluation in late spring 2018 of cough and dyspnea. Her respiratory symptoms started roughly 4 years prior to presentation, following a hospitalization for epiglottitis reportedly related to ACE-inhibitors. She thereafter developed increasing shortness of breath and cough, which were persistent. This resulted in two subsequent hospitalizations, during which time she was incorrectly diagnosed with COPD (no evidence of obstruction on spirometry in 2014) and started on supplemental oxygen therapy (2L by nasal cannula). At the time of her initial consultation, she was using budesonide and formoterol nebulizers, with rescue inhaler use about once daily. She reported using 4L of oxygen continuously while at home only. With regard to her current symptoms, she reported continued cough productive of yellow sputum, which did not improve with the addition of every other day azithromycin. She also endorsed shortness of breath made worse by exertion (with tolerance of about 100 feet), humidity, grass, pollen, and strong odors.

With regard to other past medical history, the patient was diagnosed

* Corresponding author. 110 S Paca Street, 2nd Floor, Baltimore, MD, 21201, USA.
E-mail address: jadeepak@som.umaryland.edu (J. Deepak).

https://doi.org/10.1016/j.rmcr.2020.101283
Received 8 July 2020; Received in revised form 23 October 2020; Accepted 2 November 2020
Available online 6 November 2020

with Rheumatoid Arthritis (RA) about 10 years prior to presentation. Her treatment for RA had been sporadic – she had taken methotrexate (discontinued due to persistent RA flare), mycophenolate mofetil (discontinued for unclear reasons, perhaps disease stability), hydroxychloroquine, and prednisone, but had never had rituximab. She also had stem cell therapy at some point.

The patient had a significant smoking history, having smoked 3 packs per day for 24 years, but quit roughly 20 years prior to presentation. She used alcohol socially but denied illicit drug use. She worked in a managerial position at a horse racetrack, but denied animal exposure. In the past, she had worked as a bank teller. Her home environment was notable for the possession of 4 pet birds. There was no mold exposure in the home, no one else was a smoker, and there were minimal carpets.

Her initial physical examination revealed a thin, frail, chronically ill-appearing middle-aged woman in no acute distress. Her oxygen saturation was 92% on 2L NC with normal respiratory rate, heart rate, and blood pressure. While her cardiac exam was unremarkable, her pulmonary exam revealed diffuse crackles with a prominent inspiratory squawk in the upper lung fields bilaterally. No wheezing was noted and her respiratory effort was normal. Her joint examination revealed swelling of the PIP and DIP joints of the bilateral second and third fingers without erythema, and discoloration of the finger pads consistent with mechanic's hands.

3. Investigations

Initial work-up included pulmonary function testing (PFTs), lab work, and imaging. Her first PFTs from 2014 revealed a restrictive pattern on spirometry (forced expiratory volume in 1 second, FEV1, 40% predicted and forced vital capacity, FVC, 41% predicted) in the setting of a normal total lung capacity (TLC) (Table 1). Her TLC may have been falsely elevated due to hyperinflation, as evidenced by an elevated RV which suggests the presence of obstructive disease despite a normal ratio of forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC). Over time, she did develop overt obstruction, with an FEV1/FVC ratio of 68% in 2018. At that time, her TLC again remained within the normal range but with a persistently elevated RV. Over that four year time period, her diffusion capacity (DLCO), which was initially low at 58%, worsened as well.

Laboratory testing was remarkable for an elevated serum bicarbonate of 34 mmol/L suggesting chronic respiratory acidosis and mild peripheral eosinophilia of 4.7% with otherwise normal chemistries and complete blood count. Her rheumatologic work-up revealed a positive rheumatoid factor, anti-nuclear antibody (ANA), SSA, and aldolase, but negative CCP. A myositis panel was negative, however a hypersensitivity panel was positive for reaction to pigeon antigen.

A chest x-ray from 2014 was remarkable only for flattening of the diaphragms consistent with hyperinflation. Computed tomography imaging of the chest from 2015 again showed hyperinflation with diffuse mosaic attenuation, worse during expiration (Fig. 1). This was persistent on repeat imaging in 2018 (Fig. 2). Notably absent was any evidence of emphysematous changes, focal infiltrates, upper lobe predominance, or nodularity.

Table 1
Pulmonary Function Tests (spirometry, lung volumes, and diffusion capacity) from 2014 to 2020. Values from December 2014 and June 2018 are pre-treatment. Values from September 2018 reflect two months of therapy on mycophenolate 500 mg twice daily and prednisone 15 mg daily. Spirometry from January 2020 reflects lung performance while on mycophenolate 1500 mg twice a day only. There was no reversibility demonstrated on any bronchodilator testing.

	December 2014	June 2018	September 2018	January 2020
FEV1, L (% pred)	1.12 (40%)	0.83 (36%)	1.09 (47%)	1.08 (43%)
FVC, L (% pred)	1.46 (41%)	1.24 (39%)	1.74 (56%)	1.79 (56%)
FEV1/FVC, %	77%	68%	63%	61%
TLC, L (% pred)	4.99 (97%)	5.01 (99%)	4.94 (97%)	
RV, L (% pred)	3.40 (182%)	3.67 (190%)	3.22 (165%)	
DLCO, mL/min/mmHg (% pred)	11.3 (58%)	8.6 (39%)	13.4 (61%)	

4. Differential diagnosis

Based upon the constellation of symptoms and imaging, a number of diagnoses were considered (Fig. 3). First, a range of rheumatoid arthritis-related lung disease were considered, with interstitial lung disease, small airways disease, and bronchiolitis being of chief concern. Given her exposure to birds and positive pigeon antigen, hypersensitivity pneumonitis was also considered. Prior treatment with methotrexate raised concern for delayed drug toxicity. While chronic obstructive pulmonary disease was a possibility, absence of emphysema on imaging and her pattern of symptoms made this less likely. Infection was considered less likely given the duration of her symptoms. This was a complicated case, and there were likely several concomitant diagnoses, which contributed to our treatment decisions below. However, based upon the dramatic amount of mosaic attenuation observed on CT chest imaging (particularly on expiration), lack of nodularity, and diffuse rather than upper lobe predominance on imaging, the principal diagnosis pursued was RA-related small airways disease after a multidisciplinary discussion during an institutional Interstitial Lung Disease conference. Hypersensitivity pneumonitis was also strongly considered, though imaging was rather diffuse to be entirely explained by this. Similarly, lack of emphysematous changes argued against COPD as the main diagnosis. Although there was evidence of obstruction and hyperinflation on PFTs, these could have also been a consequence of obstructive disease caused by RA rather than purely COPD. This is further supported by the fact that restrictive disease with suggestion of developing obstructive disease was present 4 years prior to presentation.

5. Treatment

A treatment approach to address the likely multifactorial disease process described above was enacted, starting with mycophenolate mofetil 250 mg, then up-titrated to 1500 mg, twice daily as immunosuppressive treatment of RA-related small airways disease. Prednisone was also included at an initial dose of 20 mg daily to treat any component of hypersensitivity pneumonitis. Over the course of a year, while increasing mycophenolate, the prednisone was tapered and eventually stopped. To treat obstructive airways disease, a combination inhaled corticosteroid and long-acting bronchodilator were also started. Additionally, the patient was educated on the importance of antigen exposure by removal of birds from the home and rehab of the existing ductal systems.

6. Outcome and follow-up

After two months on mycophenolate and prednisone, the patient returned for repeat pulmonary function testing which showed improvement of her FEV1 by 200 mL (to 1.03 L, 44% predicted) and FVC of 300 mL (1.72L 55% predicted), with stable TLC and reduced RV (3.22 L from 3.67L), as well as improvement also of her DLCO to 13.4 mL/mmHg/min (61% predicted) (Table 1). Her spirometry has remained stable now a year and a half later. Symptomatically, she has noted respiratory symptom improvement as well, and is no longer requiring daytime oxygen therapy. Her joint pains have also improved. She has successfully rehomed her cockatiels, though at the time of first follow-up she still retained one of the four birds. In spite of having the birds at

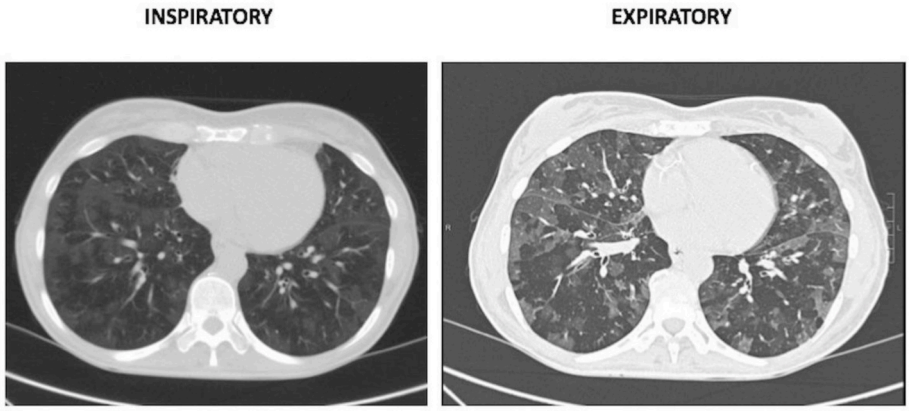

Fig. 1. Axial images from a 2015 CT chest, shown here in both inspiration and expiration, demonstrating mosaic attenuation especially during the expiratory phase, a finding consistent with air-trapping and small airways disease.

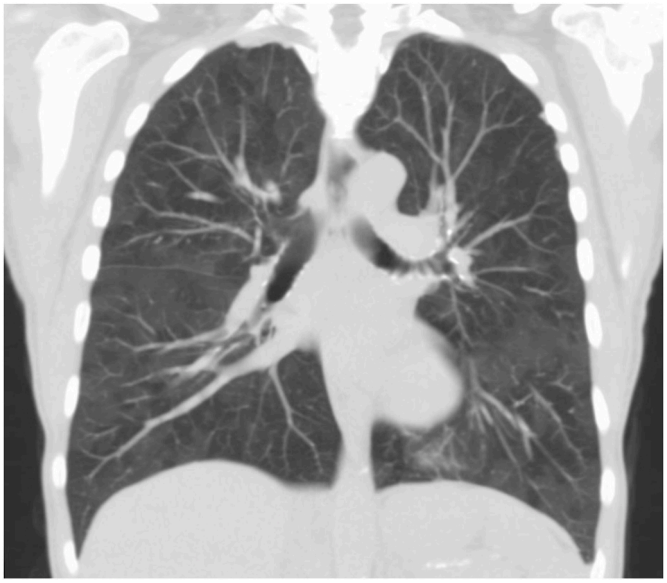

Fig. 2. Coronal images from a 2018 CT chest on inspiration, demonstrating mosaic attenuation in a diffuse distribution.

home she still had remarkable symptomatic improvement which again points towards the majority of her disease being explained by RA-related obstructive lung disease.

7. Discussion

That the diagnosis of Rheumatoid arthritis-related obstructive lung disease is challenging and often confounded in the RA population has been discussed previously. A 2013 study from the Mayo Clinic of a cohort of patients with and without RA found that the risk of RA-related obstructive disease was higher in men, current or former smokers, and in those with more severe RA [5]. However, those individuals with RA who were non-smokers did not have an increased risk of obstructive disease. In a Taiwanese retrospective cohort study, the incidence of COPD in individuals with RA was found to be 1.74 fold higher than the non-RA population; however because they used a national database that did not include information regarding tobacco use, they could not assess the effect of smoking (Shen). A prospective study of 52 non-smoking patients with "active" RA (as defined by the current use of DMARD therapy) in the United Kingdom found that there was an increased prevalence of obstructive pattern found on PFTs which did not worsen over a 10-year follow-up period [7]. These individuals did demonstrate a decline in DLCO over the same time period, which may have been attributable to their RA therapy. Even the definition of obstruction varies among these studies, with some using the traditional definition of FEV1/FVC <70% while others focused on the FEF 25–75% instead. Impulse oscillometry may be useful, where obstruction can be identified

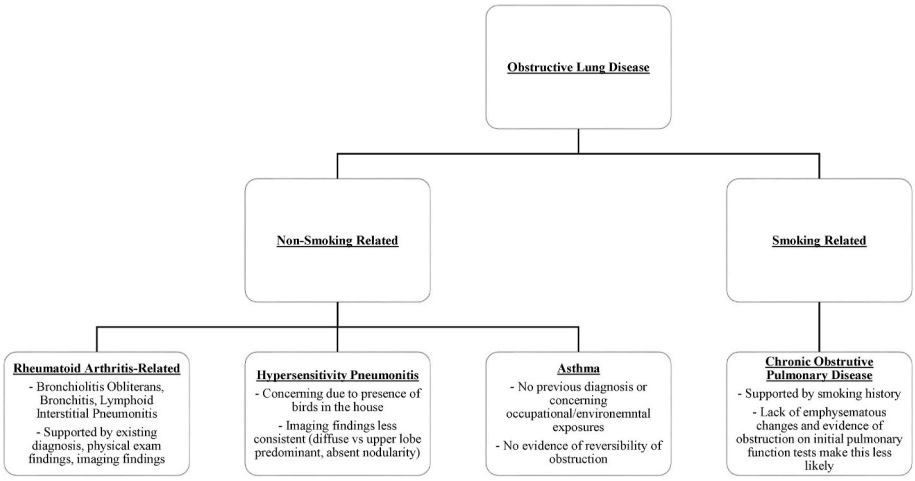

Fig. 3. Visual flowchart of potential causes of obstructive lung disease in this complex patient.

as increased resistance values at lower oscillatory frequencies. This pattern was shown to be present in a retrospective cohort of RA patients in Japan [8,9]. Overall, there is no consensus on what defines RA-related obstructive lung disease, and it should be taken into account that confounders are abundant. When the diagnosis of obstruction is made, treatment should reasonably be tried for obstructive disease with bronchodilators. If this therapy fails, or there is progression despite adequate therapy, consideration for treatment of underlying RA with DMARDs such as steroids or other immunosuppressants should be considered.

8. Learning points/take home messages

1. Rheumatoid arthritis has many different pulmonary manifestations, and can be a primary and common cause of obstructive lung disease in this patient population.
2. The high incidence of smoking in RA makes exclusion of other pulmonary diseases challenging.
3. Imaging can be helpful in distinguishing between differential diagnoses.

CRediT author statement

Danielle Glick: Conceptualization, Visualization, Writing – Original Draft; Jeffrey Galvin: Resources, Writing – Review and Editing; Janaki Deepak: Supervision, Writing – Review and Editing.

Declaration of competing interest

None.

References

[1] M. Shaw, B.F. Collins, L.A. Ho, G. Raghu, Rheumatoid arthritis-associated lung disease, Eur. Respir. Rev. 24 (135) (2015 Mar) 1–16, https://doi.org/10.1183/09059180.00008014.
[2] A. Sirajuddin, et al., Primary pulmonary lymphoid lesions: radiologic and pathologic findings, Radiographics 36 (1) (2016 Jan 12) 53–70, https://doi.org/10.1148/rg.2016140339 [Internet].
[3] H. Massey, M. Darby, A. Edey, Thoracic complications of rheumatoid arthritis, Clin. Radiol. 68 (2013) 293–301, https://doi.org/10.1016/j.crad.2012.07.007.
[4] T. Perez, M. Remy-Jardin, B. Cortet, Airways involvement in Rheumatoid Arthritis: clinical, functional, and HRCT findings, Am. J. Respir. Crit. Care Med. 157 (1998) 1658–1665.
[5] C. Nannini, et al., Incidence and mortality of obstructive lung disease in rheumatoid arthritis: a population-based study, Arthritis Care Res. 65 (8) (2013 Aug) 1243–1250, https://doi.org/10.1002/acr.21986.
[6] T.C. Shen, et al., Increased risk of chronic obstructive pulmonary disease in patients with rheumatoid arthritis: a population-based cohort study, Q. J. Med. 107 (2014) 537–543, https://doi.org/10.1093/qjmed/hcu027.
[7] J.P. Fuld, et al., A longitudinal study of lung function in nonsmoking patients with rheumatoid arthritis, Chest 124 (4) (2003 Oct) 1224–1231.
[8] R. Sokai, et al., Respiratory mechanics measured by forced oscillation technique in rheumatoid arthritis-related pulmonary abnormalities: frequency-dependence, heterogeneity, and effects of smoking, SpringerPlus 5 (2016) 335, https://doi.org/10.1186/s40064-016-1952-8 [Internet].
[9] S. Mori, K. Yukinori, M. Sugimoto, Small airway obstruction in patients with rheumatoid arthritis, Mod. Rheumatol. 21 (2) (2011 Apr) 164–173, https://doi.org/10.1007/s10165-010-0376-5.