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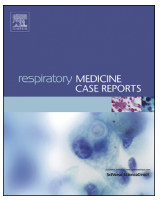

Case Report

An unexpected diagnosis of a 57-year-old women with migratory pulmonary infiltrates

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ABSTRACT

A 57-year-old female presented with sudden shortness of breath and migratory pulmonary infiltrates on imaging, which corresponds with a diagnosis of cryptogenic organizing pneumonia. Initial treatment with corticosteroids showed only mild improvement during follow-up. BAL was performed and revealed diffuse alveolar hemorrhage. Immune testing showed positive P-ANCA with positive MPO, leading to a diagnosis of microscopic polyangiitis.

1. Case presentation

A 57-year-old Caucasian female, with previous medical history of seronegative rheumatoid arthritis (RA) and iron-deficiency anemia, presented with shortness of breath and dry cough for 1 week. The patient denied fever, phlegm, hemoptysis, wheezing, chest pain, and any use of new drugs. She had never smoked and did not suffer from any allergies or asthma symptoms. Her travel history was unremarkable and she had no history of occupational, environmental, or recent animal exposure. Her room air oxygen saturation was 80%, which was well-corrected with 3 L per minute of supplemental oxygen. On physical examination she was tachypneic with 32 breathes per minute, a temperature of 36.4 C°, heart rate 67 bpm, and blood pressure 106/71 mmhg. She had diffuse fine crepitations and her finger nails were normal without clubbing or cyanosis. The rest of physical examination including skin, lymph nodes, heart, abdomen, and joints was unremarkable. Complete blood count was normal besides microcytic hypochromic anemia with hemoglobin level 9.1 mg/dl, MCV 72.2 fl, and MCH 22.9 pg. Comprehensive metabolic panel was normal including creatinine, electrolytes level, and liver function tests. C-Reactive Protein level was 5.83mg/dl. There were no acid-base abnormalities on arterial blood gases. The respiratory viruses panel, including COVID-19, was negative. Chest X-ray demonstrated para-hilar bilateral alveolar opacities with air-bronchogram, which were more dominant in the right lung fields (Fig. 1A).

The patient was admitted to the hospital and treated with 1 Gram Ceftriaxone and 500 mg Azithromycin for suspected pneumonia. After 3 days without any clinical improvement, a second chest X-ray was done that showed partial resolution in the para-hilar opacities with new upper fields opacities (Fig. 1B). A CT imaging of the chest was performed that showed bilateral non-homogenous pleural based opacities, mostly ground glass and some alveolar, a reverse halo sign, and bronchus dilation (Fig. 2 A + C).

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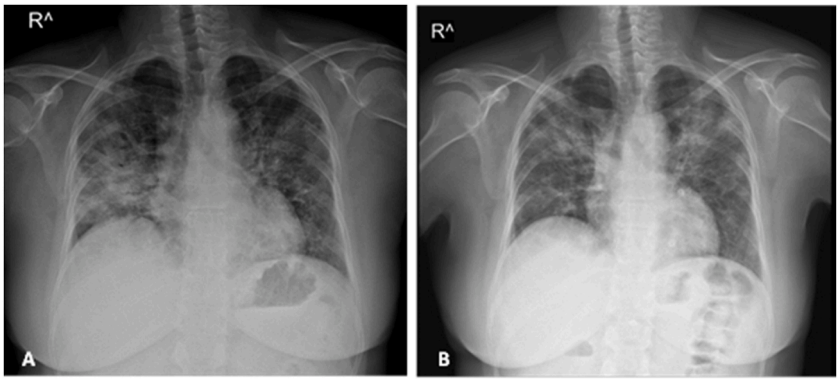

Fig. 1. Chest X-ray at days 1 and 3.
Chest X-ray shows para-hilar bilateral alveolar opacities with air-bronchogram (A). Chest X-ray taken three days later shows some resolution of the previously seen para-hilar opacities but new upper fields opacities have emerged (B).

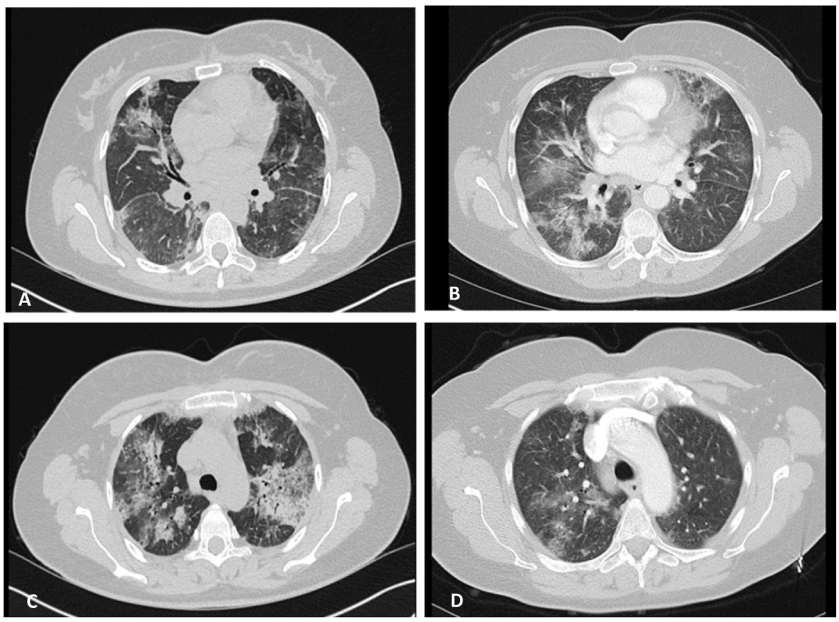

Fig. 2. Chest CT taken four months apart (A + C on the left column on August 21 and B + D on the left column on January 22).
Chest CT shows the pattern of infiltrating opacities coincides with the diagnosis of organizing pneumonia. Images A + B at the height of the left atrium. Image B showing new patchy infiltrates in the RLL and lingual. Images C + D at the height of the aortic arch. Image C showing bilateral non-homogenous pleural based opacities, mostly ground-glass and some alveolar. Image D shows significant resolution of the opacities.

Antibiotic treatment was withheld and 40 mg of prednisone was initiated for a diagnosis of Cryptogenic Organizing Pneumonia (COP). Gradually the patient demonstrated some clinical improvement and was discharged with 40 mg prednisone, home-supplemental oxygen, and a referral to an out-patient pulmonary clinic.

The patient presented to our pulmonary clinic 1 month after discharge with a slight clinical improvement. On physical examination she had decreased breath sounds on lung auscultation. Room air saturation was 95% but after climbing ten stairs her saturation dropped to 86%. Updated chest x-ray showed significant improvement (Fig. 3A) and saturation while breathing room-air was 95%; however, after a mild effort of 25 stairs it dropped to 86%. Pulmonary function test indicated an FEV1 to FVC ratio of 89%, FEV1 55% of predicted, and FVC 52% of predicted, with a restrictive-shaped flow-volume loop. Lung volumes were low with total lung capacity and residual volumes of 45% and 60% of predicted, respectively. Her diffusion capacity of the lungs for carbon monoxide (DLCO) was 55% of predicted. The patient was instructed to continue 40 mg of prednisone daily. The follow-up visit and assessment in the pulmonology clinic revealed deterioration in pulmonary function tests: FEV1 and FVC were both 32% of predicted, and FEV1 to FVC ratio was 86% and DLCO 31% of predicted. An updated chest X-ray revealed patchy infiltrates in the right lung regions and alveolar opacities in the left field (Fig. 3B). A second chest CT was performed which demonstrated patchy non-homogenous opacities in different lung regions, with some resolution of previous opacities (Fig. 2B + D).

Due to lack of clinical improvement with prednisone and the nature of the pulmonary infiltrates, a bronchoscopy with bronchoalveolar lavage (BAL) and cryobiopsy were performed. BAL return was blood tinged with increasing bloody return on three sequential

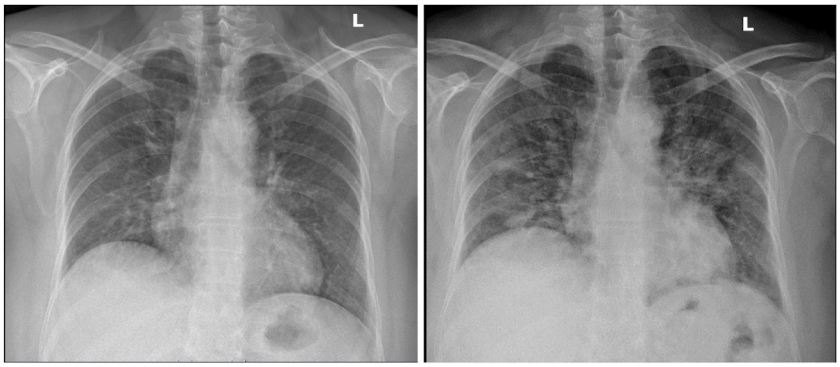

Fig. 3. Image A showing a significant improvement after 1 month of prednisone treatment. Image B taken 3 months later while continuing prednisone shows radiologic worsening with new patchy bilateral opacities, more dominant in the right lung fields.

aliquots. Cell count showed 90% neutrophils, 1% lymphocytes, 2% eosinophils, and 7% macrophages. Cytology BAL fluid findings reveled a large population of hemosiderin stained macrophages. Pathology findings from the cryobiopsy reveled intra alveolar hemosiderin-laden macrophages, mild septal thickening, and foci of chronic inflammation. A few tiny foci suspicious for organizing pneumonia were seen. Immune testing showed positive P-ANCA, positive MPO, negative C-ANCA, and negative Anti-GMB; tests for ANA profile, rheumatoid factor, and ACPA were negative; and levels of complement were normal. A diagnosis of microscopic polyangiitis (MPA) was made. The patient was started on a steroid pulse (1g of methylprednisolone per day for 3 days) and 1 g of cyclophosphamide infusions monthly, which led to fast clinical and radiologic improvement (Fig. 4).

1.1. Clinical results

The case presented herein started as a rather common clinical scenario with a patient presenting with acute shortness of breath and bilateral fleeting pulmonary infiltrates. The fact that the patient had no hemoptysis during her clinical course, normal blood tests including kidney function, no eosinophils on blood or cell count from BAL, and no symptoms or signs of systemic illness along with the described radiologic pattern led to the diagnosis of COP. Radiologic improvement with corticosteroids reinforced this working diagnosis. Diffuse alveolar hemorrhage (DAH) was not considered due to lack of hemoptysis, respiratory stability, and preserved well-being of the patient, along with the rapid improvement of the patient's condition after few days of a relatively low dose of corticosteroids. Furthermore, the CT image did not correlate with the diagnosis of DAH. Rheumatoid arthritis can be an etiology for migratory pulmonary infiltrates [1] in general and specifically for organizing pneumonia [2]. However, our patient had seronegative RA, which is less likely to cause lung involvement. Furthermore, the acute presentation and radiologic did not fit RA associated ILD. During the clinical course, the patient had a fluctuating pattern of clinical improvement and deterioration while being treated with a relatively long course of corticosteroids. This pattern raised our concern regarding the working diagnosis of COP, which is typically initially highly sensitive to corticosteroids, and led us to continue with invasive procedures. A differential diagnosis of "partially resolved with steroids" pulmonary infiltrates can be challenging and includes, among others lymphoma, DAH, different connective tissue diseases, and in rare cases vasculitis [3]. Signs of macro and microscopic alveolar hemorrhage on BAL, presence of intra-alveolar hemosiderin-

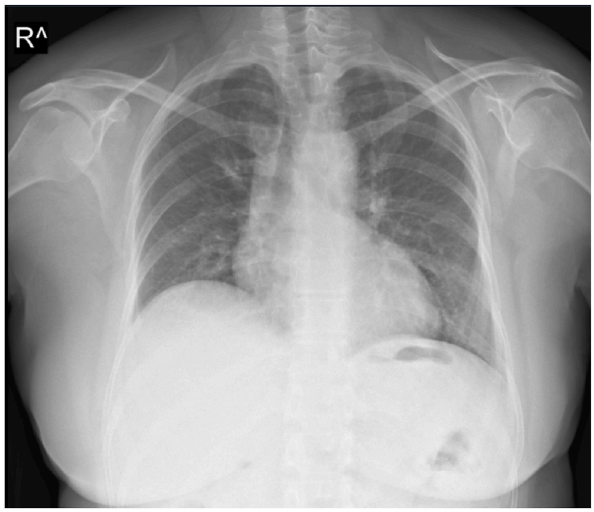

Fig. 4. X-ray showing marked resolution of previously seen pulmonary infiltrates after Pulse Solumedrol and Cyclophosphamid treatments.

Table 1
Differential diagnosis of pulmonary migratory opacities.

Organizing Pneumonia (OP)
Eosinophilic Pneumonia (EP)
Eosinophilic granulomatosis with polyangiitis (EGPA)
Allergic bronchopulmonary aspergillosis (ABPA)
Diffuse alveolar hemorrhage (DAH)

laden macrophages, only mild septal thickening, and foci of chronic inflammation on cryobiopsy, along with the positive serological results of P-ANCA, allowed us to conclude that organizing pneumonia was the presenting syndrome, co-existing with DAH due to an underlying pulmonary ANCA associated-vasculitis. This rather unique finding of microscopic polyangiitis presenting as organizing pneumonia is an example of the many "hats" that organizing pneumonia can "wear" and the necessity of becoming familiar with the differential diagnosis of secondary organizing pneumonia, before deciding to name it cryptogenic.

1.2. Radiologic features

The appearance of pulmonary migratory infiltrates is neither a rare radiologic finding nor pathognomonic. Table 1 lists the differential diagnosis of pulmonary migratory infiltrates; OP is most probably the most common when presenting with pulmonary migratory opacities.

In our case, few radiologic features were unique for organizing pneumonia (cryptogenic or secondary). The "reverse halo sign", also known as "Atoll sign", is one of the most suggestive radiologic findings for organizing pneumonia. Although it may appear in other diseases such as opportunistic fungal invasive infections (e.g., invasive mucormycosis and aspergilosis), another form of ANCA associated vasculitis including granulomatous with polyangiitis (GPA), sarcoidosis, tuberculosis, radiation pneumonitis, acute pulmonary Covid-19, and neoplasm is mostly seen in organizing pneumonia. Reverse halo sign (or Atoll sign) was prominent in our patient' CT images (Fig. 2A). Other radiologic findings supporting OP were also seen, such as sub-pleural triangle shaped opacities, bronchial wall irregularities, and bronchial dilatation (Fig. 2); all, in addition to the reverse halo sign, strongly suggesting diagnosis of OP. Absence of a history of bronchial asthma and of peripheral and bronchial (according to BAL) eosinophilia allowed us to rule out eosinophilic pneumonia and EGPA, with the proviso of possible influence of steroids on eosinophil count under steroid therapy. DAH, which is the pulmonary hallmark of ANCA associated vasculitis, usually appears on chest CT as ground glass opacities with random distribution but normally will not show a "wax and wane" pattern (i.e., migratory) or include other radiologic features, as seen in OP as discussed above. Allergic bronchopulmonary aspergilosis (ABPA) can present with migratory infiltrates on imaging but our patient did not have asthma nor cystic fibrosis, and no peripheral or bronchial eosinophilia were found in the BAL fluid.

1.3. Pathologic features

Typical histologic features of pulmonary involvement of MPA include diffuse alveolar hemorrhage (fresh blood in alveolar spaces and/or hemosiderin-laden macrophages in alveolar spaces), neutrophilic capillaritis, features of diffuse alveolar damage, or acute fibrinous organizing pneumonia. Moreover, interstitial fibrosis may be evident in subsets of patients [4–6]. The microscopic analysis of lung cryo-biopsy samples demonstrated mainly intra alveolar hemosiderin - laden macrophages with only mild septal thickening and foci of chronic inflammation (Fig. 5). There were no prominent classical features of vasculitis, probably due to the long period (more than 4 months) of previous steroid treatment. These findings, together with cytology analysis of the BAL fluid showing leukocytes and macrophages with hemosiderin, support the evidence of alveolar hemorrhage which along with the evidence of few foci suspicious for OP, supported the fact that OP coexisted with the vasculitic process, as was suspected initially.

2. Discussion

The clinical features (progressive dyspnea with hypoxemia), radiologic (migratory pulmonary infiltrates) and pathologic findings (DAH), together with positive P-ANCA provided the diagnosis of MPA. The inflammatory process formally termed BOOP (bronchiolitis obliterans organizing pneumonia) which for several years is termed COP (cryptogenic organizing pneumonia) holds a somewhat controversial terminology for many of the OPs are not "cryptogenic" but rather secondary to an underlying process such as infections, drugs, malignancies and, as on our case, vasculitis [2]. In our patient, clinical presentation and imaging findings were highly supportive of OP but the clinical course did not fit well with the common clinical course of COP. Due to patient's clinical deterioration while being treated with corticosteroids, further investigation was mandatory. BAL and cryo-biopsy results, along with the presence of P-ANCA, allowed us to conclude that OP was a rare presenting feature of a more serious, systemic illness, MPA.

3. Conclusion

This case stressed the importance of being aware that COP may also be secondary OP as a presenting feature of other systemic diseases with different treatment approach and sequelas.

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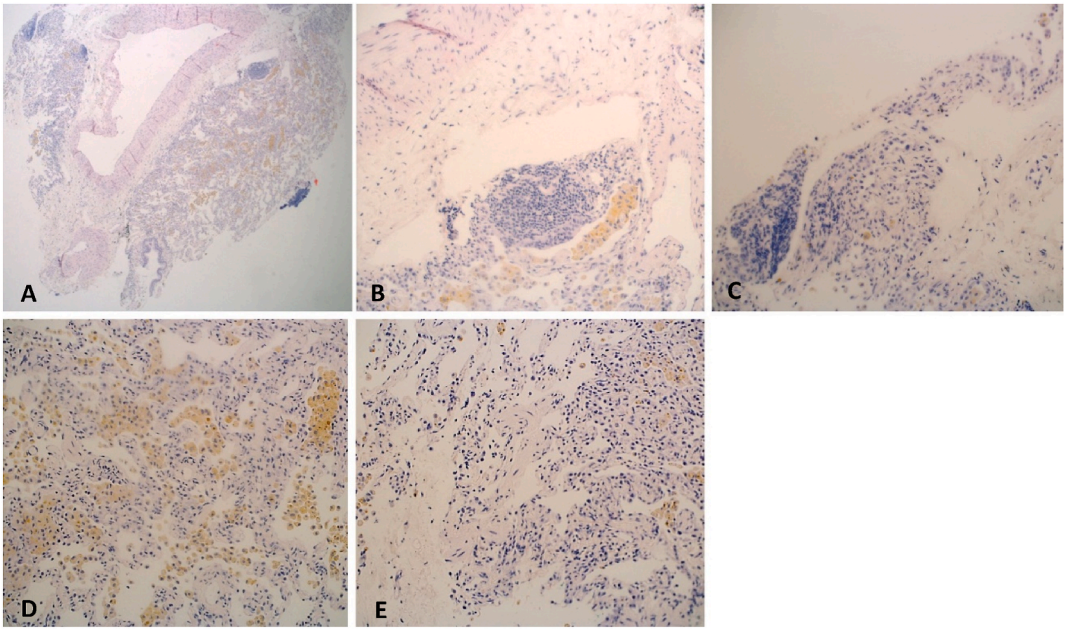

Fig. 5. Histological analysis of the lung biopsy.
H&E stained section in lower magnification (A) and high power magnification (B-E) shows alveolar hemosiderin - laden macrophages, mild septal thickening, and foci of chronic inflammation. Few foci suspicious for organizing pneumonia are seen.

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Declaration of competing interest

The authors have no conflicts of interest to declare. We have no sources of funding and/or study sponsors to report.

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