An Interesting Case of Bilateral Lung Consolidation

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Abstract
Organising pneumonia is a histopathological entity characterised by intra-alveolar buds of granulation tissue, intermixed myofibroblasts and connective tissue. Cryptogenic organising pneumonia (COP) is characterised by this particular histopathological pattern, along with typical clinical and imaging features, when no other underlying aetiology is found. COP (previously known as bronchiolitis obliterans organising pneumonia [BOOP]) is one of the rare variants of interstitial pneumonias. This condition is characterised by a rapid clinical and radiological improvement with steroid treatment. Here we are reporting a case of COP in adult female with discussion on approach and basic pathophysiology of this type of pneumonia.

Introduction
Organising pneumonias (OP) usually present with non-specific symptoms, radiographic and pulmonary function test (PFT) findings. The cause can be primary (cryptogenic organising pneumonia [COP]) or secondary (secondary OP). Cryptogenic organising pneumonia is classified under idiopathic interstitial pneumonia. Secondary causes of OP include infections, connective tissue diseases, drugs, malignancies, organ transplantation, aspiration and radiation injury. It is important to make such distinction as the management of secondary organising pneumonia involves treatment of the underlying disease or potential avoidance of the offending agent. It is often associated with poor prognosis and is less responsive to treatment as compared to COP.

Case and Discussion
A 55-year-old housewife, a known diabetic, presented to the outpatient department of All India Institute of Medical Sciences (AIIMS) hospital, New Delhi with 4 month history of cough and high grade fever. The cough was dry in nature, no diurnal or postural variation and without any significant aggravating or relieving factors. Patient had complaints of weight loss of about 4 kgs over last one month. She also had progressive shortness of breath for last 1 month, which had progressed from mMRC (modified medical research council) grade 1 to grade 4 over 1 month. She was a known diabetic since last 7 years and was on oral hypoglycemic agents. She had history of exposure to passive smoking and exposure to chulha for 20 years in the past. There was no history suggestive of connective tissue disease, exposure to fumes, dust or working in the farm. At the same time her husband was diagnosed to have extra-pulmonary TB (tubercular pleural effusion).

At admission, she was febrile with temperature of 100°F. Blood pressure was 110/70 mmHg with pulse rate of 110/min. Respiratory rate was 30/min with use of accessory respiratory muscles and visible intercostal recession. The SpO₂ was 80% on room air and 96% on oxygen (O₂) at 6 litres/minute via face mask. Patient was pale, however, there was no icterus, clubbing, cyanosis, lymphadenopathy, skin rash or pedal edema. The ocular and fundus examination was normal. Examination of upper respiratory tract, oral cavity, tonsils and posterior pharyngeal wall was normal.

Laboratory investigations revealed haemoglobin – 12.6 g/dl, total leucocyte count – 14.6 x 10³/mm³, platelet count – 490 x 10³/mm³ and erythrocyte sedimentation rate

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- 102 mm at the end of 1st hour. Chest X-ray revealed bilateral lower and mid zone air-space opacities (Figure 1). Differential diagnosis considered were pulmonary tuberculosis, bacterial/fungal pneumonia, lung carcinoma (bronchoalveolar variant), hypersensitivity pneumonitis and sarcoidosis were considered.

Liver and renal functions were in normal range with exception of reversal of albumin:globulin ratio. Electrocardiogram (ECG) and 2D-echocardiography (ECHO) were within normal limits. Arterial blood gas (ABG) analysis revealed pH – 7.40, PaCO₂ – 30.8 mmHg, PaO₂ - 55.6 mmHg, HCO₃⁻ – 20.3 mmol/L with FiO₂ – 0.4. Alveolar (A) to arterial (a) oxygen gradient was 196 mmHg (normal value - 5 – 20 mmHg) suggestive of pulmonary parenchymal pathology. Normal (A-a) gradient adjusted for age can be calculated as estimated (A-a) gradient which is (4 + age in years/4).¹ (A-a) gradient helps in differentiating the extra-pulmonary causes of respiratory failure from those involving parenchymal lung disease. In extra-pulmonary failure, the (A-a) gradient remains normal. In cases of shunt, diffusion impairment or ventilation-perfusion (V-Q) mismatch, the gradient is usually elevated. Hypoxemia due to V-Q mismatch or diffusion impairment can be corrected with supplemental oxygen while that due to right-left shunt cannot. (A-a) gradient is also a measure of the severity of gas exchange impairment and is used as guide for steroid therapy in cases of Pneumocystis carinii pneumonia.

HIV ELISA was negative. Autoimmune work-up in the form of rheumatoid factor (RF), p-ANCA and c-ANCA and double stranded (ds) -DNA was negative. Anti-nuclear antibody (ANA) was positive in 1:40 titer with speckled pattern. Positive titres of less than 1:160 can be present in up to 20% of the healthy elderly population. Titres more than 1:160 are seen in up to 5% of normal adult individuals. Serology for Aspergillus and Histoplasma was negative. Serum lactate dehydrogenase (LDH) and angiotensin converting enzyme (ACE) levels were within normal limits. Serum C - reactive protein (CRP) was elevated. Sputum smear examination with Gram stain and acid-fast bacilli (AFB) stain was negative. High resolution computed tomography (HRCT) of the chest (Figure 2) revealed areas of bilateral lower zone consolidation mainly involving peri-hilar areas, without any surrounding ground-glassing with presence of reverse-halo sign suggesting organizing pneumonia. Reverse halo sign is characterized by presence of central ground-glass opacity surrounded by area of consolidation. It was first described as a specific sign for COP, however it has been reported in a variety of pulmonary diseases including invasive fungal pneumonias, tuberculosis, granulomatous polyangiitis, lymphomatoid granulomatosis and sarcoidosis.² Based on this revised differentials of pulmonary tuberculosis (spouse diagnosed as TB, systemic symptoms, elevated ESR, imaging compatible), bacterial pneumonia (sick, elevated total peripheral blood counts, imaging compatible), sarcoidosis (though serum ACE was normal and HRCT was not typical, alveolar sarcoid still a possibility), limited Wegener’s (ANCA can be negative), and cryptogenic organizing pneumonia (age group compatible, subacute presentation, imaging compatible) were kept.

CT-guided lung biopsy was
done. Biopsy revealed thickening of inter-alveolar septae along with chronic inflammatory cell infiltrate (Figure 3A) and type II pneumocytes proliferation with intra-alveolar smooth muscle bundles proliferation forming a ball-like structure (Masson body) (Figure 3B) which is a characteristic finding of organizing pneumonia.

A final diagnosis of COP was made in view of characteristic clinical, radiological and histopathological features with no other secondary cause.

The term ‘cryptogenic organizing pneumonia’ (COP) was introduced by Davison et al in 1983. It was later supplanted in the American literature by the term ‘BOOP.’ In 2002, the American Thoracic Society/European Respiratory Society International Consensus Panel for the Classification of Idiopathic Interstitial Pneumonia (ATS/ERS) recommended the term ‘COP’ be used as preferred clinical term for idiopathic cases, emphasising the cryptogenic nature of the process. COP is characterised by insidious onset, non-specific physiologic findings, and variable radiographic patterns, but with typical histopathologic findings that are sine qua non for diagnosis. It is important to remember that COP is a diagnosis of exclusion and secondary causes (Table 1) should be ruled out before making final diagnosis. Patients usually experience a 2–10 week prodrome prior to seeking medical attention. The disease has no sex predilection and occurs usually in 6th decade, although paediatric cases have been reported. No predisposing factors have been identified and, in particular, organising pneumonia is not related to smoking in comparison to other ILDs like respiratory bronchiolitis-associated interstitial lung disease, desquamative interstitial pneumonia, and pulmonary Langerhans cell histiocytosis. COP should be included in the differential diagnosis in any patient with bilateral airspace disease that is unresponsive to antibiotics.

The typical imaging characteristic of COP is of multiple patchy alveolar opacities with a peripheral and bilateral distribution. These opacities may migrate spontaneously. Their size is often variable and can range from a few centimetres to a whole lobe. Two other patterns include solitary opacity (focal COP), and infiltrative opacities (infiltrative COP). This imaging pattern, although highly suggestive of COP, is not specific and the differential diagnosis on imaging include conditions such as the primary-low grade pulmonary lymphomas, chronic eosinophilic pneumonias (which can occur with COP), and bronchioloalveolar carcinoma. Pulmonary functions reveal mild to moderate restrictive defect, with minimal or no airflow obstruction and reduced carbon monoxide diffusion capacity. No specific lab findings are observed in COP. Patients usually have raised ESR and CRP with neutrophilic leucocytosis more so in secondary OP. The gold standard for diagnosis is video-assisted thoracoscopic lung biopsy, as it provides large lung specimens allowing diagnosis to be made with confidence and other pathological features can also be searched. Trans-bronchial lung biopsy specimens are inadequate for excluding secondary causes.

Treatment decisions are based on clinical experience and observations from case series because of lack of randomized trials. The decision to initiate treatment and choice of initial therapy depends on severity of symptoms, extent of disease on imaging and rapidity of progression. In patients with minimal symptoms and mild radiographic involvement it is reasonable to monitor abnormalities at 8 to 12 weeks interval. In patients with mild to moderate symptoms treatment with macrolides is an option, particularly for those
who chose to avoid steroids.\textsuperscript{5} Clarithromycin 250 to 500 mg twice a day has been used in few cases. Corticosteroids is the treatment of choice in patients with persistent or progressive disease. The ideal dose and duration of steroids in COP is not well-defined. Clinical improvement is seen within 48 hrs, while radiological resolution takes several months. The recommended daily dose of steroids is 0.75 – 1 mg/kg of prednisone and usual duration is six to twelve weeks.\textsuperscript{6} COP is associated with frequent relapses involving initial or different sites and some patients require prolonged treatment with steroids. In such cases steroid-sparing agents in from of azathioprine and cyclophosphamide can be used. The prognosis of typical COP with patchy alveolar involvement is usually good.

Our patient was started on 60 mg (1 mg/kg) prednisone initially which was tapered over next 3 months. Subsequently, she was shifted to steroid-sparing agent in the form of azathioprine due to development of side effects of steroids. At the end of 6 months, she was doing well with remarkable relief in fever, weight loss, shortness of breath and cough. Her diabetic status is also well controlled. Investigations showed normalization of ESR, CRP and albumin:globulin ratio. Arterial blood gas (ABG) analysis on room air revealed pH – 7.42, PaCO\textsubscript{2} – 32.5 mmHg, PaO\textsubscript{2} - 66.5 mmHg. D (A-a) O\textsubscript{2} was 44 mmHg compared to 194 mmHg at the time of presentation (Table 2). Both chest X-ray and HRCT (Figure 4) showed significant resolution. The patient is currently on follow-up in the outpatient department.

**Conclusion**

COP is one of the rare idiopathic interstitial pneumonias and remains as diagnosis of exclusion. Patient is labelled to have a COP based on clinical, radiological and characteristic histological findings only after excluding secondary causes. A careful history of occupation, exposure to dusts, fumes, therapeutic radiation and history suggestive of connective tissue diseases should be elicited as other pulmonary pathologies such as chronic eosinophilic pneumonia, hypersensitivity pneumonitis or diffuse alveolar damage can have similar radiological and histopathological findings.

**References**