RCPE Challenging cases

1. Basic case vignette

History:

A 51 year old lady presents to the medical admissions unit (MAU) with a 4/52 history of increasing SOB (she is now SOB on minimal exertion), non-productive cough, occasional sweats, fever and pleuritic chest pain. In addition she is nauseated, exhausted and lethargic. Her GP had been treating her with erythromycin for a presumed lower respiratory tract infection but this had made no difference.

Her past medical history is significant only for a previous road traffic accident with neck injury and her regular medication includes: Paracetamol 1g qds tramadol 50mg qds and gabapentin 100mg tds

She drinks approximately a bottle of wine/week and is an ex-smoker of 5 years (15 pack year history).

Examination reveals an alert and orientated lady speaking full sentences though noticeably breathless at rest.

Vital Signs:

Temperature 36.8oC
Blood pressure 109/73mmHg
Heart rate 82bpm
Oxygen saturations 94% on room air
Respiratory rate 28

Respiratory System**:**
Coarse crackles at left base with decreased air entry bibasally
Not finger clubbing, calves soft and non-tender
Cardiovascular, gastrointestinal and neurological systems examine normally

Questions

What further information should be sought from the history?
What would you include in your initial differential diagnosis?
What investigations would you like to perform?
Justify your investigation strategy

Discussion

The DDx is not currently wide. The presentation seems entirely compatible with community-acquired pneumonia that has not responded to initial antibiotic therapy.

Different pathogens may be responsible in such a case:
Bacterial: Streptococcus pneumoniae, Haemophilus influenzae, mycoplasma pneumoniae, legionella pneumophila, staphylococcus aureus (potentially MRSA or PVL toxin producing)
Viral: Influenza viruses, adenovirus, rhinovirus, metapneumovirus, respiratory syncitial virus
Mycobacterial: M. tuberculosis, M.avium complex,
Fungal: Actinomycosis, nocardiosis, pneumocystis

In this setting it is always important to consider that an underlying disease might be predisposing to the development of pneumonia. Thus, the possibility of a chronic respiratory disease e.g., COPD, bronchiectasis, asthma or a cause of immunosuppression e.g., HIV (where background prevalence is above then all patients admitted with pneumonia should have HIV testing), malignancy. The patient should be asked about risk factors for immunosuppression including: recreational drug abuse, sexual behaviour and systemic symptoms (weight loss, night sweats, malnutrition).

When a patient with significant smoking history develops pneumonia the potential for a post-obstructive pneumonia in the setting of a new bronchial malignancy should be considered.

It will be important to establish whether the patient has recently travelled abroad or whether they have been exposed to family members, work colleagues or acquaintances with similar symptoms. It is also important to document a full occupational history and to ask about exposure to animals or birds at home, work or recreationally.

Investigations should now include venous bloods (FBC, U+Es, LFTs, Glucose, CRP and Calcium), arterial blood gases, chest x-ray, blood cultures, throat swab for viral PCR and sputum for MC&S (should sputum become available). A urinalysis would also be valuable.

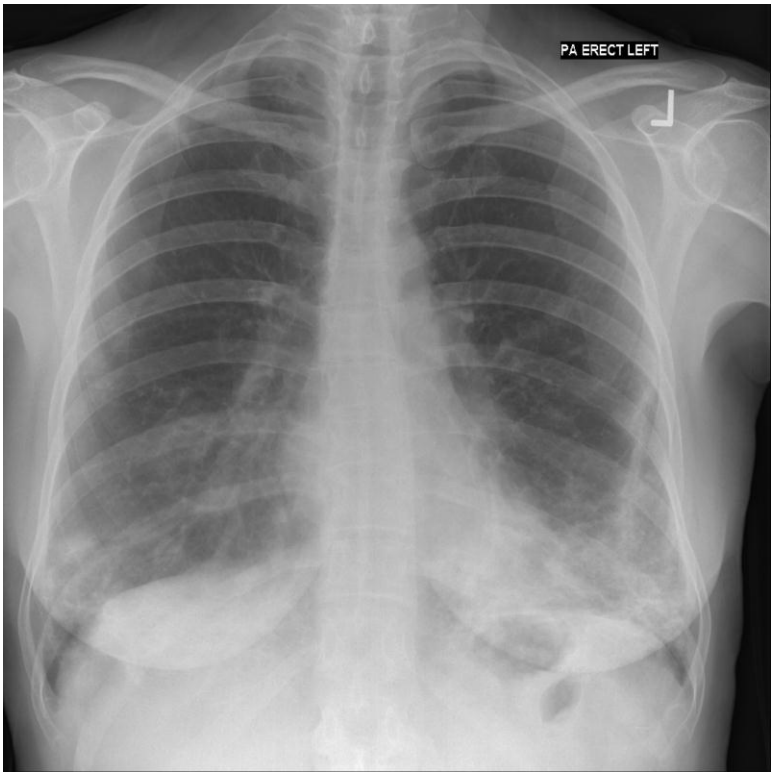
Venous bloods will detect anaemia as a cause of breathlessness or as part of an underlying malignancy, they will show the immune response to a pathogen (neutrophilia, neutropenia) and will allow CURB65 (Urea) risk stratification. LFTs can be deranged in sepsis and pneumonia but may also be affected by antibiotics so it is good to establish a baseline. CRP will show whether there is an acute phase response in progress and persistent elevation at 1 week may indicate treatment failure. Every effort should be made to establish a causative pathogen. Urinalysis may indicate an alternative source of sepsis, vasculitis or significant proteinuria (as a cause of immunosuppression). Chest x-ray is required to diagnose pneumonia.

2. Initial Investigations

Venous Bloods:
Haemoglobin 12.2g/l
White cell count 9.34
Neutrophils 6.69 + normal differential),
Platelets 460
CRP 22
U+E's/LFT's/Bone/Glucose all within normal range

Arterial blood gases (on 2litres O_2 via nasal cannulae)
pH 7.43, pCO2 3.4, pO2 11.2, Bicarb 21, SaO2 97%
Urinalysis: no significant proteinuria, haematuria, leucocytes or nitrites detected

Chest X-ray



CXR Report

There is patchy consolidation bibasally particularly at the left base where the left heart border is obscured (suggesting involvement of the lingula). There is a streaky, peripheral vertical shadow at the left base to mid-zone and the appearance of a nodule overlying the 7th anterior rib on the right. There is a suggestion of reticulo-nodular pattern bilaterally.

The differential diagnosis still includes pneumonic consolidation though the reticulonodular appearance may suggest an underlying interstitial lung disease. The CXR is well-inspired and it could be argued hyperinflated as a 7th anterior rib is visible above the diaphragm on the right. Any nodule-type appearance even in the presence of overt pneumonia requires careful radiographic follow-up to resolution.

On balance, despite the lack of fever, normal white cell count and unimpressive CRP, antibiotics covering the majority of common pneumonia pathogens should be started whilst awaiting further results. There should now be a suspicion that pneumonia may not be the correct diagnosis. A wider differential based on the initial investigations and specifically considering the chest x-ray appearances might include:

- **Patchy consolidation**
  - **Pneumonia**
  - **Pulmonary oedema**
  - **Cryptogenic organizing pneumnia**
  - **Pulmonary haemorrage**
  - **Drug-related pneumonitis**
  - **Malignancy (bronchoalveolar carcinoma, lymphoma)**
- **Interstitial shadowing - Interstitial lung diseases (ILD)**
  - **Idiopathic pulmonary fibrosis (IPF)**
  - **Asbestosis**
  - **Connective tissue disease (CTD) related ILD**
  - **Acute/Chronic hypersensitivity pneumonitis (HP)**
  - **Drug-induced interstitial lung disease**
  - **Sarcoidosis**

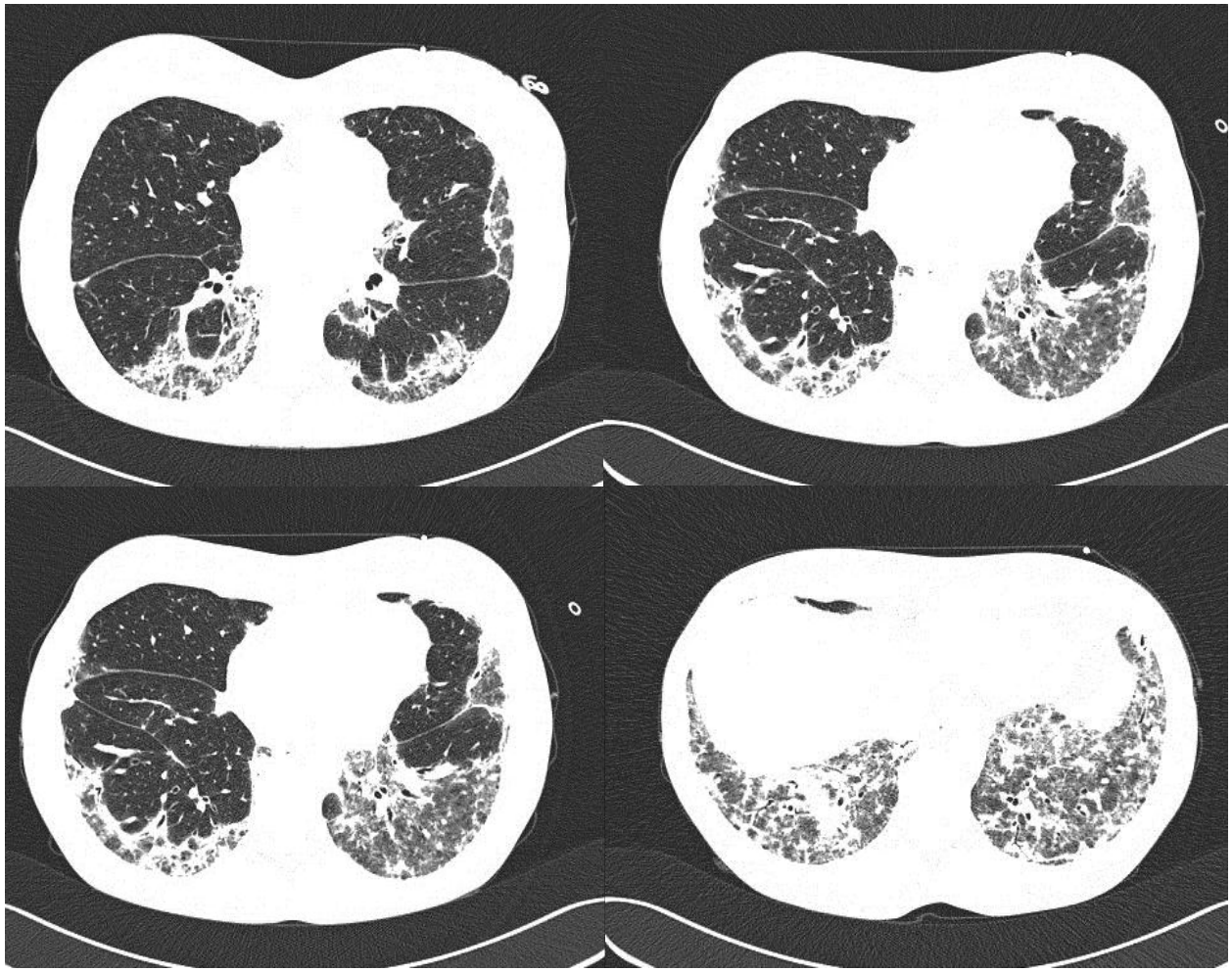
Progress

The patient fails to improve after 10 days of antibiotic therapy. She still feels terrible has ongoing cough, pain and subjective fever (though temperature is always within normal limits). She now requires 28% oxygen to maintain her oxygen saturations. A throat swab for respiratory pathogen PCR reveals no viruses, PJP, mycoplasma pneumoniae or legionella and induced sputum results are also negative. A bronchoscopy performed 48hrs earlier (when induced sputum returned negative) shows no pathogens (samples sent for MC+S, Virology, Mycology, PJP and AAFB/Mycobacterial culture). The lavage cytology has been reported as a non-specific inflammatory/reactive type picture. HIV test was negative. Inflammatory markers are unchanged from admission.

What investigation would you perform now?

3. Further examination finding/ further information from history/Further investigation

At this stage with a non-resolving pneumonic picture with no clinical improvement (in fact a deterioration) no confirmed causative pathogen and an atypical chest x-ray appearance it is reasonable to proceed to HRCT scanning. Arguably, a CTPA might be a useful investigation.



Questions
What does the HRCT show?
What does your differential diagnosis include now?
What further investigation should now be performed?

4. Final results section

HRCT/CTPA report:

Predominantly peripheral fibrosis and ground glass opacification
Associated scarring and bronchial distortion but no honeycombing
No significantly enlarged mediastinal lymph nodes
No pulmonary thromboembolism

The differential diagnosis now changes significantly:

Cryptogenic organising pneumonia
NSIP
IPF (atypical)
Chronic eosinophilic pneumonia

Any of the above + unidentified infection

The most important further investigation is a surgical lung biopsy though a full connective tissue disease and vasculitis screen should be undertaken.

VATS lung biopsy report
organising pneumonia

HISTOLOGY PICTURE HERE WOULD BE GOOD

Connective tissue disease and vasculitis screen negative

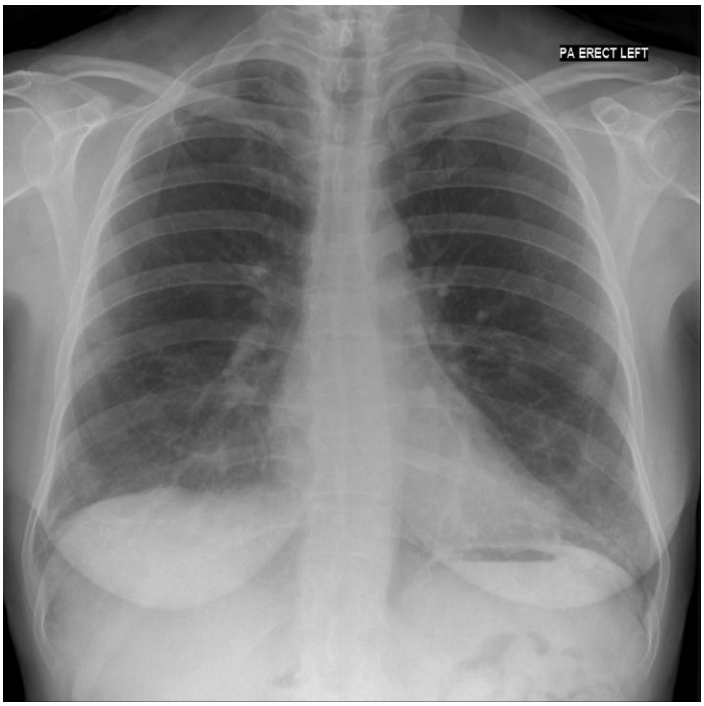
Diagnosis: Cryptogenic organising pneumonia (COP)

Question:
How would you treat this condition?

Answer: First line treatment is high-dose corticosteroids – the patient was started on 60mg prednisolone/day. The steroid dose can be gradually reduced over time but maintenance therapy is likely to continue for at least 1 year. Consideration should be given to gastric and bone protection whilst on long-term steroids.

Progress

The only post-operative complication was pain and a few days after initiation of steroid theroxygen saturations were 97% on room air, although there was still evidence of desaturation after mobilisation. The patient was discharged 1 week later with short burst oxygen and 2/12 post-discharge she no longer required oxygen and was feeling much better having regained her appetite and some weight. Chest x-ray was much improved (see below), spirometry better FEV1 2.8l/ VC 3.3l (previous 1.7l/2.2l) and oxygen saturations 97% on room air. She continues on a slowly, reducing regime of prednisolone (currently 15mg OD).



6. Educational information about the case

Cryptogenic organizing pneumonia

The histological diagnosis of organizing pneumonia is felt to result from the failure of normal resolution of inflammation within lung tissue after an insult. Histologically, it is defined by the presence in distal air spaces of buds of granulation tissue which progress from fibrin exudates to loose collagen containing fibroblasts. There are several known causes of organising pneumonia (see list).

Infections
Bacterial e.g. strep. Pneumoniae, 'atypicals'
Viral e.g. Influenza, CMV
Fungal e.g. crytococcus neoformans, Pneumocystis jiroveci
Parasites e.g. Plasmodium vivax

Drugs
Several case reports for different medications, see pneumotox.com
Radiotherapy
Connective tissue disorders
Post-transplant (lung, BMT)
IBD
Haematological malignancies

When there is a histological diagnosis of organising pneumonia and no known cause or association the condition is termed cryptogenic organising pneumonia (COP) or idiopathic BOOP (I-BOOP). There is no predilection of the condition for either sex (M:F = 1:1) and the median age of onset is 50 – 60yrs. It is more common in non-smokers.

<u>Presentation of COP</u>

- **'**Flu-like' illness/'pneumonia not resolving with Abs'
  - Fever
  - Cough
  - Malaise
  - Progressive dyspnoea – severe in rapidly progressive disease
  - Anorexia and weight loss
- Uncommon features
  - Haemoptysis
  - Chest pain, night sweats
  - mild arthralgia (significant arthralgia may represent CTD)
  - Persisting air-leak following pneumothorax
- Diagnosis often delayed given non-specific (6–13 weeks).
- Examination may be normal or show some sparse crackles without finger clubbing.

<u>Imaging Characteristics of COP</u>

3 described patterns on CXR/HRCT

- 'typical COP': multifocal consolidation, bilateral/peripheral and can be migratory
- 'focal COP': solitary pulmonary mass – may be mistaken for lung Ca (can cavitate; PET +ve)
- 'infiltrative COP': interstitial pattern superimposed on alveolar opacities

Other important investigations

- Lung function testing
  - Intrapulmonary restriction with reduced transfer factor and relatively normal transfer coefficient
- Bronchoalveolar lavage
  - Useful to rule out infection or malignancy
  - White cell differential shows mixed picture, lymphocyte predominant
- Bloods
  - Neutrophilia
  - Increased inflammatory makers

Management of COP

- Usually responds very well to high dose steroids (0.75 – 1.5mg/kg prednisolone) with gradual reduction over time
- No specific treatment period but usually requires long duration of steroids to avoid relapse e.g. 1 year
- Relapse rate reported between 13 – 58%
- Little evidence for other immunosupressives

Learning Points

- **To consider COP in patients with non-resolving pneumonia picture**
- **Radiological pattern of COP can include a 'fibrotic' looking picture**
- **COP can only be confirmed after other aetiologies/associations of organising pneumonia have been excluded**
- **BAL/transbronchial biopsy are helpful in excluding other diagnoses but surgical lung biopsy is most helpful in confirming diagnosis**
- **Usually responds very well to prolonged steroids with little lung damage if treated promptly**

7. MCQs testing learning from the case

7a. What treatment is indicated for COP?

1. None
2. Lower dose steroids (e.g. 10 – 20mg prednisolone)
3. Higher dose steroids (e.g. 50 – 60mg prednisolone)
4. Azathioprine
5. Cyclophosphamide

- First line is high dose steroids – patient started on 60mg prednisolone/day

7b. Regarding organising pneumonias, which of the following is not a cause/association?

1. Legionella
2. Influenza
3. PCP
4. Amioderone
5. ACE-i
6. Radiotherapy

7c. Regards cryptogenic organising pneumonia, which of the following is false?

1. Smokers are affected more than non-smokers
2. Radiological appearances can include a solitary focal opacities
3. Radiological appearances can include infiltrative pattern (interstitial opacification)
4. In a series of patients with ILD, correct diagnosis of COP was made on HRCT images in around 80% of cases
5. BAL shows a mixed cell differential pattern with the majority of cells lymphocytic

8. Further reading :

- Cryptogenic organising pneumonia. Cordier JF. *Eur Respir J. 2006 Aug;28(2):422-46*
- Cryptogenic organising pneumonia in: Oxford Desk Reference – Respiratory Medicine (N. Maskell, A. Millar) published by OUP