Question 100

A 65 year old man presents with a 2 month history of non-productive cough, dyspnoea on exertion and low grade fevers. His medications include simvastatin, aspirin, atenolol, amiodarone and enalapril. On examination, he is afebrile, the JVP is not raised and cardiac examination is normal. There are crackles over the lower half of both lung fields. His chest X ray is shown below.

Pulmonary function tests show a moderate restrictive defect with a marked reduction in diffusion capacity for carbon monoxide. There is a mild neutrophil leucocytosis and an ESR of 55 mm/hr (normal 0-13)

The most likely diagnosis is:

A. Sarcoidosis
B. Amiodarone toxicity
C. Cryptogenic fibrosing alveolitis
D. Atypical pneumonia
E. Cardiac failure

Answer: B

All of the above diagnoses are reasonable, helpful if it specified the presence/absence of clubbing

A. Sarcoidosis
   - Tends to affect young adults, blacks > whites
   - Pulmonary fibrosis of upper zones
   - CXR findings (4 stages) but most typically bilateral hilar lymphadenopathy and reticulate interstitial opacities in **UPPER zones**
   - Can present with fever, but usually with arthralgia and rash (erythema nodosum)
   - Causes low white cell count (5-10%), ESR may be high , ACE level may be high

B. Cryptogenic fibrosing alveolitis
   - ie Idiopathic pulmonary fibrosis (rarest of all listed)
- Problems with classification
- Histopathological diagnosis ("usual interstitial pneumonia" on lung biopsy)
- Major and minor criteria
- Usually affects men, age 40-70 years (mostly > 60 years old, increased incidence w age)
- Insidious and usually present > 6/12 of symptoms
- CXR usually abnormal with bibasal interstitial opacities (if alveolar, it’s something else)

D. Atypical pneumonia
- Again a possibility but 2 month history of untreated pneumonia without progression makes it less likely

E. Cardiac failure
- probably the strongest ddx but would probably expect a bit of RV failure and a raised JVP
- Cardiomegaly on CXR but likely pre-existant – based on his medications one would deduce that he has CCF (metoprolol and enalapril); no upper lobe diversion
- ACE inhibitors may cause a cough (up to 20% affected between 1/52 to 6/12 of commenced, high prevalence in Chinese ie up to 50%) through accumulation of kinins (increased prostaglandins that stimulate afferent C fibres) which are usually metabolized by ACE

Amiodarone pulmonary toxicity (< 5% on amiodarone affected)

- DIAGNOSIS OF EXCLUSION
- Other Ddx: PE and lung cancer
- Prognosis generally good
- ≤ 10% mortality rate unless ARDS (mortality around 50%)
- Correlates with cumulative dose rather than drug levels
- Usually presents months to years after initiation (though case reports of fulminant course over days)
- Lipophilic and thus accumulates in many tissues: half life 25 –100 days

- Risk factors:
  1) Total cumulative dose over months to years
  2) Underlying lung disease (no recommendations, reported in some case series but one prospective RCT vs placebo with 519 patients found no accelerated loss of DLCO among COPD patients)
- Treatment: stopping drug +/- prednisolone 50mg daily

4 main types

1) Interstitial pneumonitis
   - commonest
   - insidious onset of cough, dyspnoea +/- weight loss
   - bilateral interstitial infiltrates on CXR

2) Organizing pneumonia
   - seen in 25% (mimics chest infection)
   - more acute onset of cough, dyspnoea, fever +/- pleuritic chest pain
   - patchy alveolar infiltrates on CXR

3) Acute respiratory distress syndrome (ARDS)
   - rare but may be fatal, poorest prognosis
   - usually post-operative (thoracic surgery) or pulmonary angiography

4) Solitary lung nodule
   - uncommon, ddx cancer

Main symptoms and signs
- 50-75%: Unproductive cough and dyspnoea (especially on exertion)
- 30-50%: Fever, weight loss and malaise
- Bilateral crepitations
- No clubbing (clubbing usually present in restrictive lung diseases)

**Laboratory markers**
- Often non-specific
- ↑ white cell count, ESR and LDH
- Serum amiodarone levels often within therapeutic range
- No eosinophilia
- Negative vasculitic screen
- Potential use of glycoprotein KL-6 ie mucin secreted by proliferating Type 2 pneumocytes (case report measuring serum KL-6 showed 5X elevation in those with toxicity compared to those with pneumonia, CCF or lung cancer)

**Imaging**
- CXR: localized or diffused alveolar +/- interstitial opacities, may be migratory and can occur in absence of symptoms
- CT chest/abdomen: increased attenuation of chest/ liver and spleen due to high iodine levels (but does not ddx between toxic vs normal accumulation)

**Others**
- Bronchoalveolar lavage: no particular cellular pattern, increased foam cells
- Lung biopsy: mostly used to exclude cancer
- RFT: non specific, usually abnormal in those with amiodarone but if DLCO decreases > 20% should be further investigated

Other side effects of amiodarone:
- Thyroid dysfunction (both hyper and hypothyroidism; generally must have underlying dysfunction)
- Cardiotoxicity (low pro-arrhythmia risk eg torsades < 1%, sinus bradycardia)
- Hepatotoxicity (rise in AST, need to stop if > 2x elevation)
- Ocular changes (corneal microdeposits, optic neuropathy)
- Skin reactions (photosensitivity, slate grey skin from deposition of lipofuscin)
- GI effects (usually during loading dose)
- Neurotoxicity (tremor, ataxia)
- Sterile epididymitis
- Increases serum cholesterol, HDL and TAG
- Many drug interactions