FOOL'S GOLD?

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Mrs KT

- 42 year old woman born in Ireland
- Pmhx:
  - Juvenile arthritis / Psoariatic arthritis
    - Dx Age 14
    - Involved small joints of hands, wrist, knees
    - Well controlled since commencing Adalimumab in 2008
      - Functional improvement
      - Minimal analgesia : paracetamol, occasional celecoxib
      - No prednisolone

Mrs KT

- Presented with a 3 week illness
- Week 1:
  - Fevers to 39 C, night sweats,Lethargy
  - Mild SOB, non productive cough
  - CXR: no consolidation
  - ALP 138, GGT 129, CRP 61
- Week 2:
  - Ongoing fevers, night sweats, increasing SOB, non productive cough
    - Dx with LRTI
    - Commenced on Augmentin
- Week 3:
  - LOW 4kg over 3 week period
  - Admitted to Epworth for further investigation on 20/6/11

Mrs KT

- O/E
  - Not unwell, dry cough
  - T37.8°C, Sat 93% RA
  - Chest: bibasal creps

- Bloods
  - FBE – 120/4.8 (**lymph 0.6**)/230
  - LFTs – alb **36** ALP **411** GGT **636** ALT **61** AST **41** Bili 6
  - CRP – **147**, ESR – **66**
  - Blood cultures – (negative)

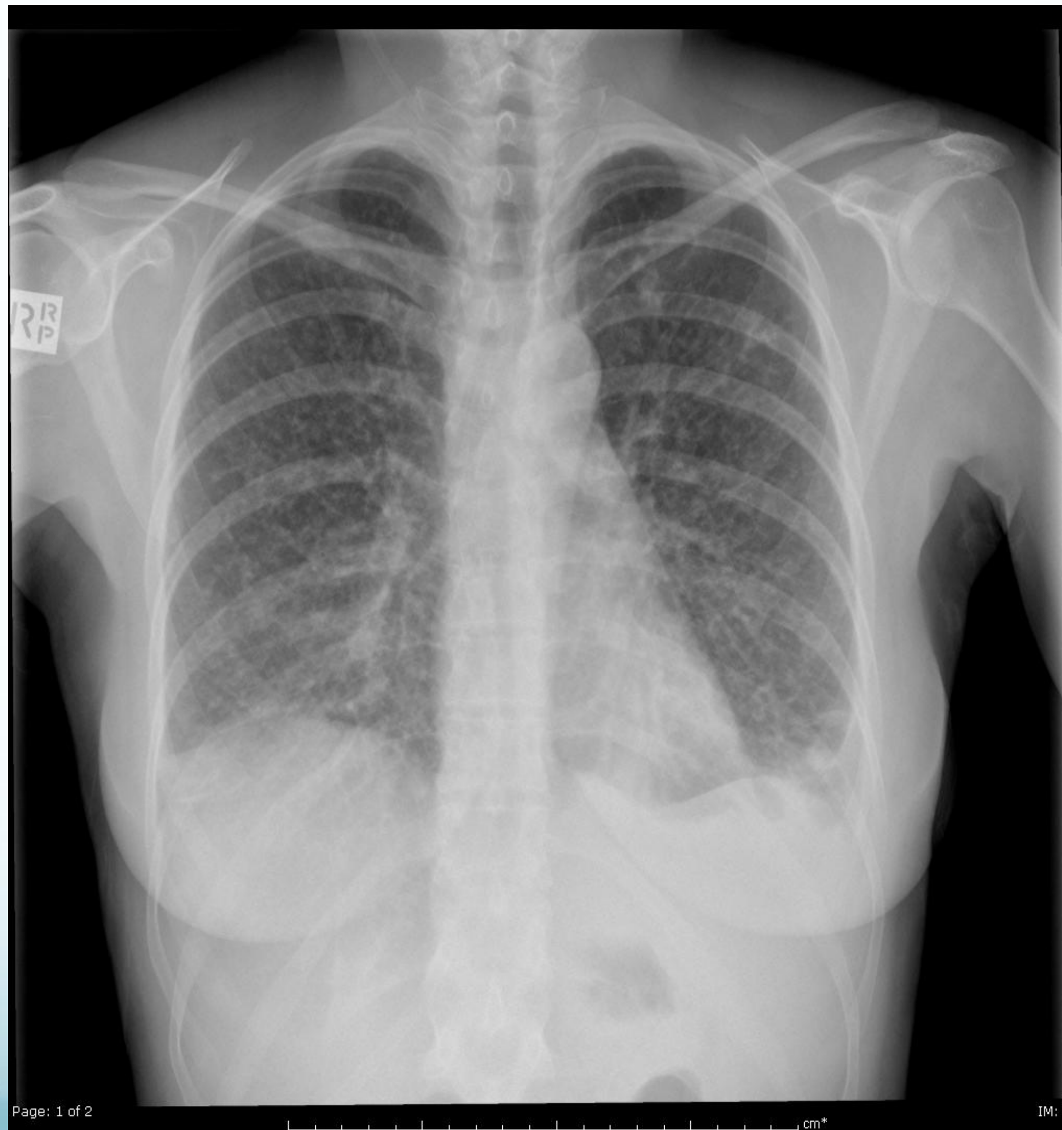
Mrs KT

- Differential diagnosis?

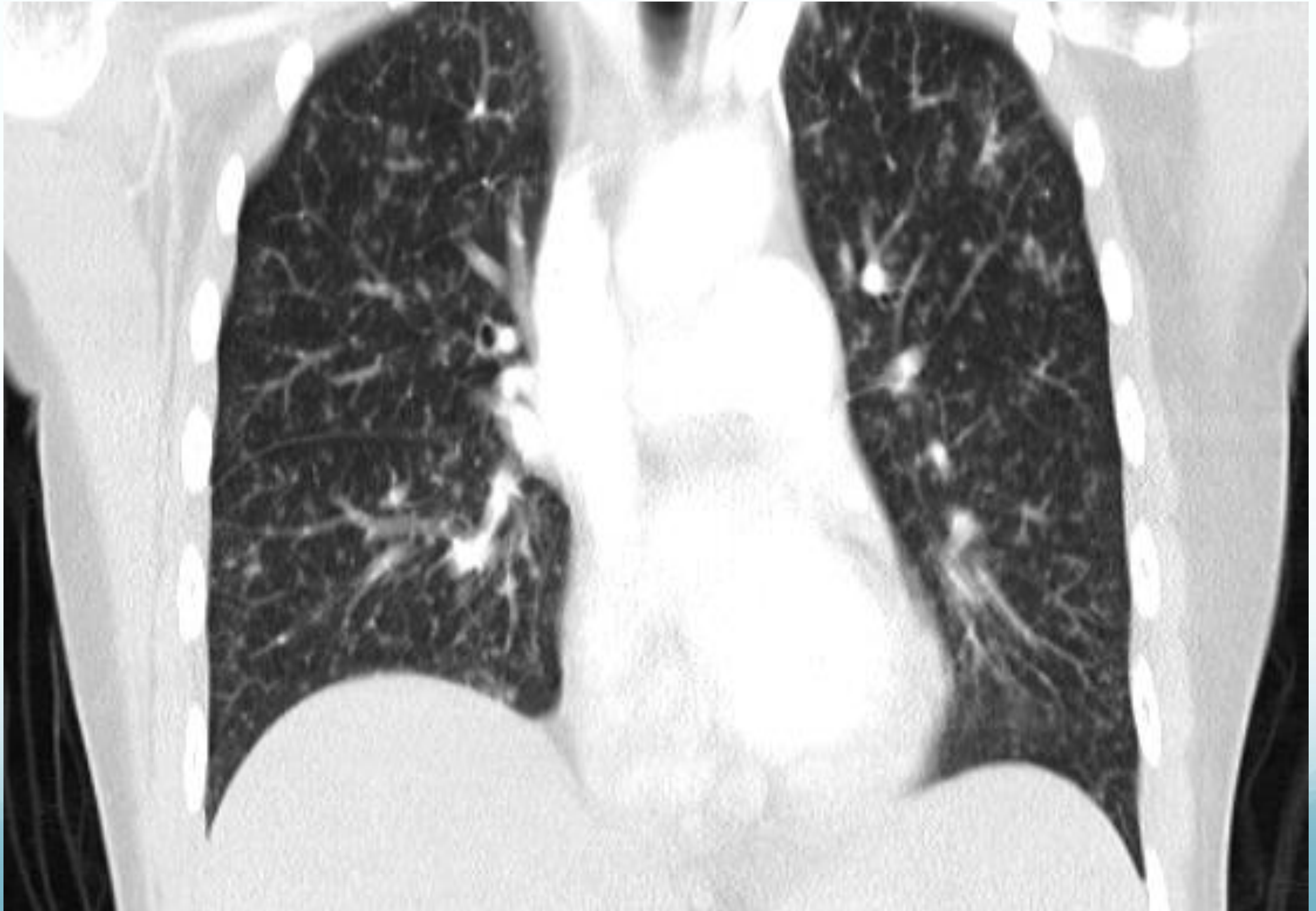
Mrs KT

- Differential diagnosis:
  - Atypical pneumonia
  - PJP
  - Autoimmune process ?pneumonitis
  - TB

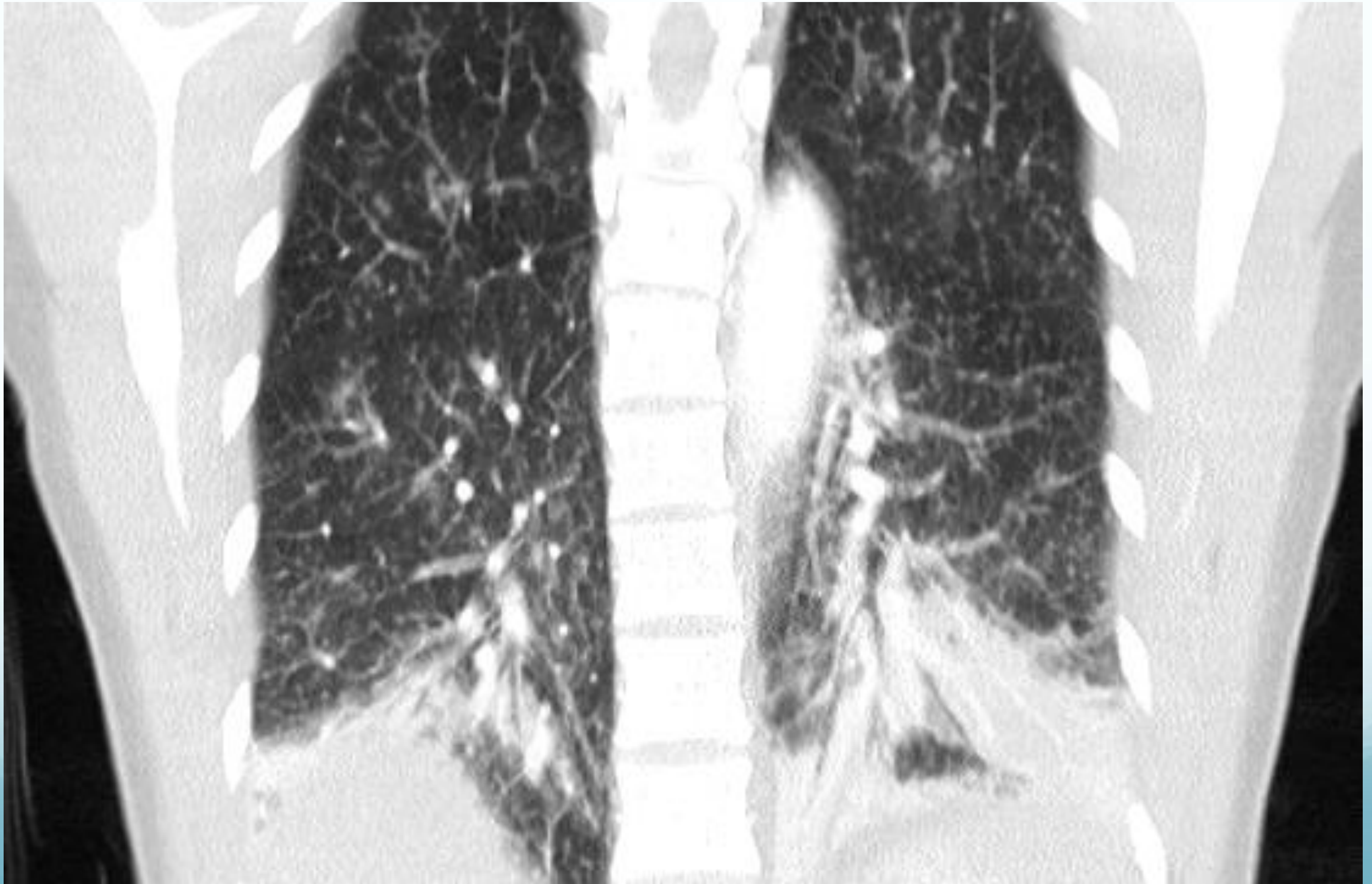
Mrs KT



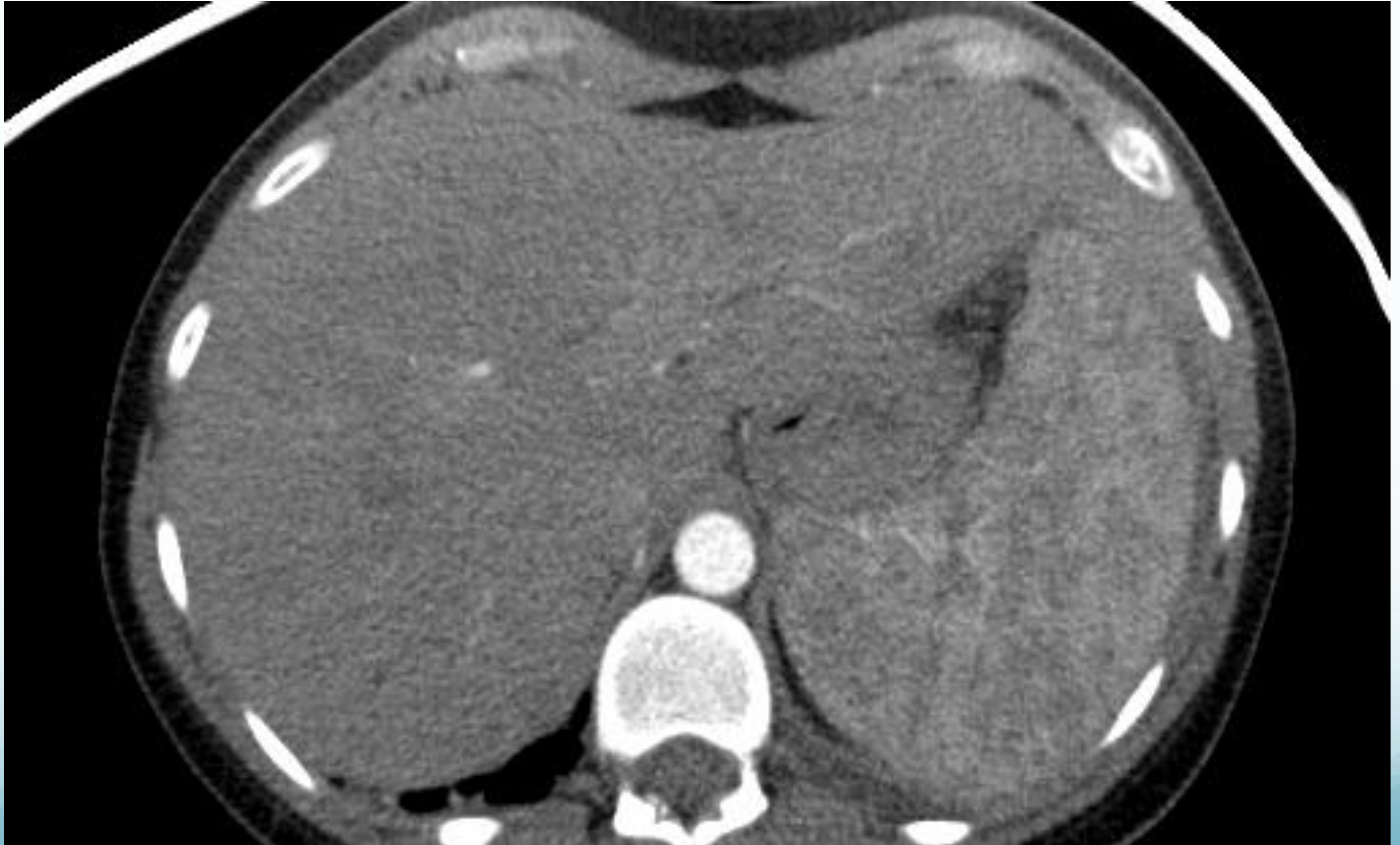
Mrs KT



Mrs KT



Mrs KT



Mrs KT

- Possible Miliary TB
- Transfer to RMH on 22/6/11 for:
  - Negative pressure isolation
  - Further investigation and management

Mrs KT

- TB risk factors:
  - Born Ireland, migrated when 3/12 old
  - No personal history of TB
  - Step brother
    - pulmonary TB age 12
    - Travelled to Estonia, Yugoslavia
    - Not in the same household
  - Screened with TST (neg), CXR (NAD) and had BCG vaccination
  - Pre commencement with adalimumab (2008)
    - Screened with IGRA (neg)
    - CXR – no abnormalities detected

Mrs KT

- Negative pressure isolation
- Bronchoscopy 24/6
  - BAL cytology: lymphocytosis, no granulomas, no malignant cells
  - Negative: resp viral PCR, PJP, adenovirus,
  - Smear neg
  - TB PCR and MPT64 antigen positive
  - Culture (subsequently): MTB

Mrs KT

- Commenced on HRZE with clinical response
  - Improved oxygenation
  - Resolution of fevers and sweats
  - Cough settled
  - LFTs stable with treatment
- Discharged home
- Repeat IGRA: positive (0.9, with mitogen response)

Mr RA

- 55 year old Philippino man
- PMHx:
  - Hepatitis B
    - HepBsAg pos, HepBeAg pos, HepBeAb neg
    - HBV DNA VL 17 X 10^6 IU
  - Psoariasis
    - Extensive cutaneous involvement
      - Dermatology reviews
    - Small joints of the hand
    - Managed with Methotrexate 30mg/weekly, no prednisolone

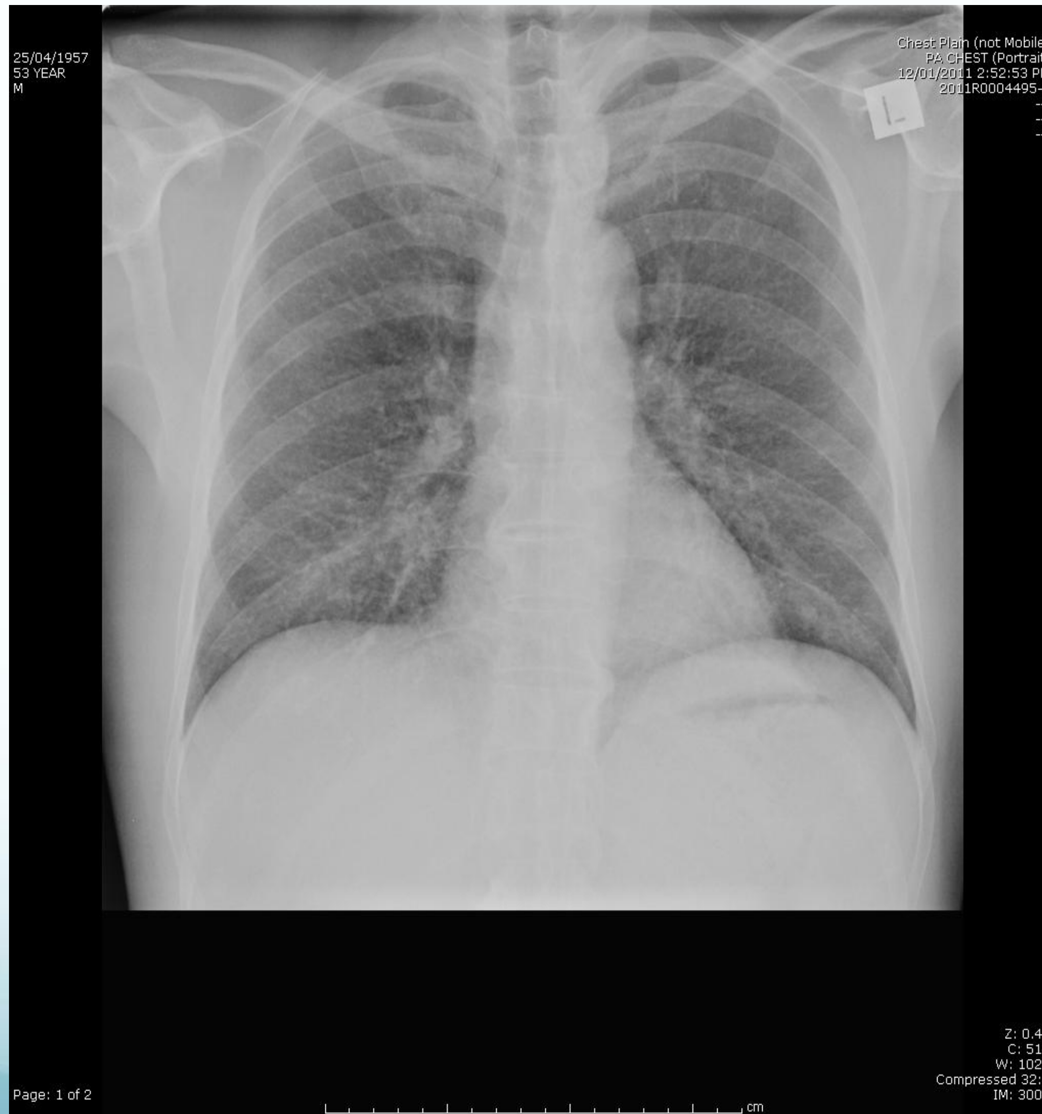
Mr RA

- For commencement of anti-TNF
- Commenced on entecavir June 2009
  - Undetectable VL prior to anti-TNF commencement
- Screened for TB:
  - Risk factors
    - Born in Philippines
    - No personal Hx, family Hx, contact Hx of TB
    - Migrated 2001, no recent return trip
  - CXR: no abnormalities, no granulomas
  - IGRA negative (no levels)

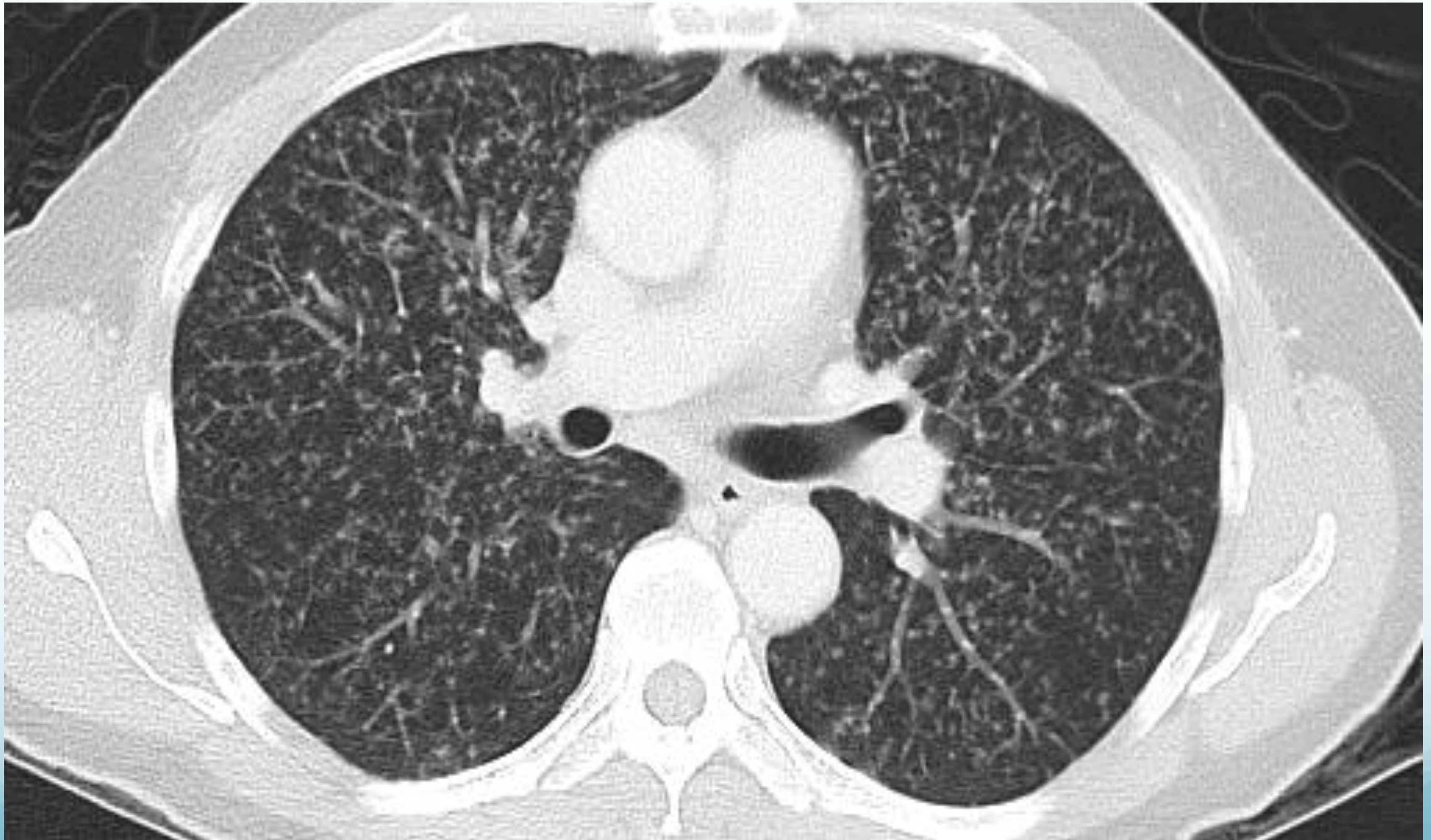
Mr RA

- Progress:
  - 16/2/10 : commenced on infliximab
    - 5mg/kg on week 0,2,6,14
  - June 2010: Returned to the Philippines for a visit
    - No TB contacts
  - 15/11/10:
    - Presented with 2/52 of fevers and night sweats and 1/52 of non productive cough

Mr RA



Mr RA



Mr RA

- Diagnosed with miliary TB
- Commenced on HRZE on 19/11/10
- 3/12/10:
  - Sputum: smear neg, culture positive MTB
- 6/1/11:
  - MDR TB (Rif/INH resistant)
  - HR ceased, moxifloxacin and amikacin commenced
- 29/7/11:
  - Amikacin ceased, MZE for further 12/12
- Repeat IGRA: negative (0.10, mitogen response)

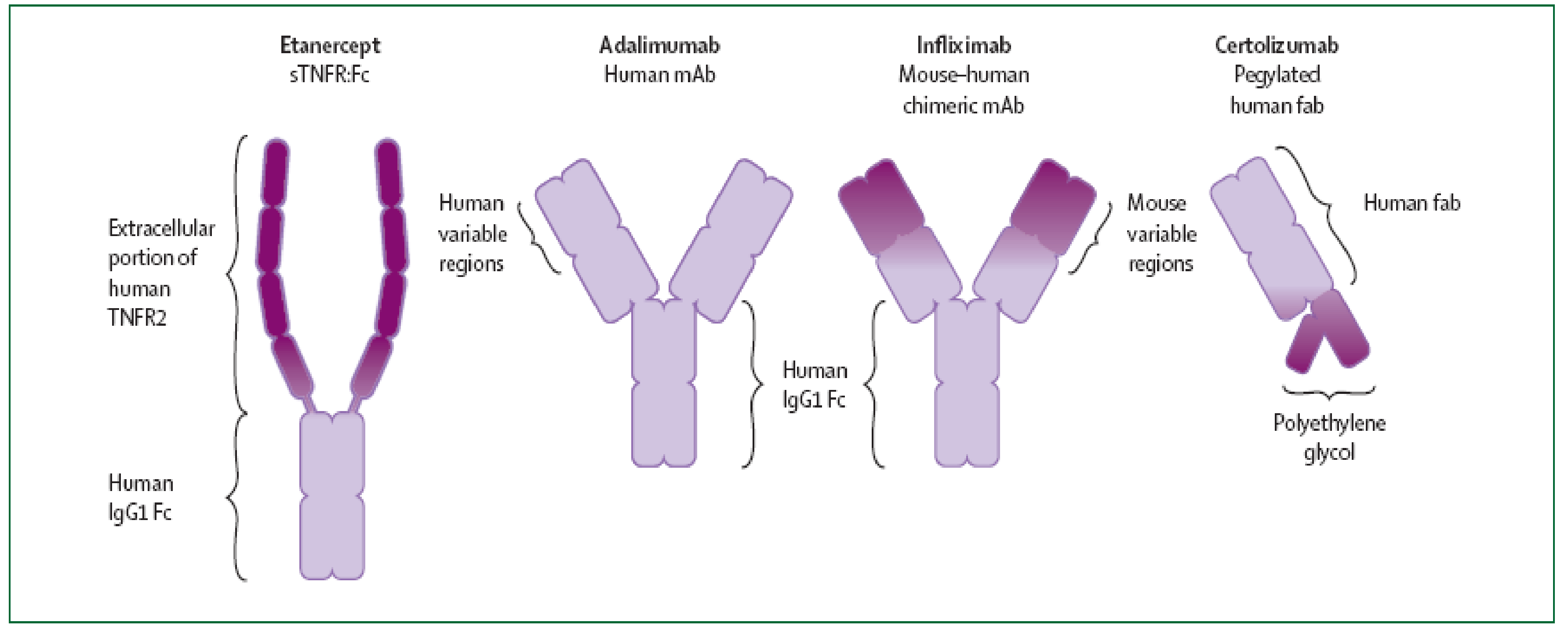
Summary

- 2 cases of disseminated (miliary) TB:
  - Anti-TNF therapy (Adalimumab/Infliximab)
  - TB risk factors:
    - Contact Hx
    - Country of birth & recent travel
  - Negative screening investigations
    - CXR : no evidence of past TB
    - TST and IGRA negative (Mrs KT)
    - IGRA negative (Mr RA)

Discussion

- Anti-TNF agents and infective risk
- Screening for LTBI prior to anti-TNF therapy
  - Guidelines
  - Compliance with screening
- Additional screening measures
- Outcomes with treatment LTBI

Anti-TNF



Lancet Infect Dis. 2008 Oct;8(10):601-11

Infection risk

- Anti-TNF associated with increased risk of:
  - Skin and soft tissue infections
  - Infections with intracellular pathogens
    - Listeria, Salmonella
  - Serious infections
    - IV Abx, admission, death
    - 1st 6 months
  - Mycobacterium tuberculosis
    - Up to 5 fold increased risk
    - Loss of macrophage activation, recuitment and granuloma integrity

Rheumatology 2011;50 (1): 124-131.
JAMA. 2006;295(19):2275-2285
Thorax. 2005;60:800-805

TB reactivation risk

- Are all anti-TNF agents equal?
- 3 to 4 times higher rate in infliximab and adalimumab compared with etanercept
- Median time to event:
  - 5.5 months infliximab
  - 18.5 months adalimumab
  - 13.4 months etanercept

TB reactivation risk

- Site of TB, extrapulmonary in:
  - 67% infliximab
  - 65% adalimumab
  - 28% etanercept
- Of the TB cases, disseminated in:
  - 17% of infliximab related cases
  - 40% of adalimumab related cases
  - 13% of etanercept related cases

Ann Rheum Dis. 2010 Mar;69(3):522-8

Screening LTBI

- Treatment of LTBI decreases incidence of active TB >80%
- Guidelines
  - BTS
    - Assessment of TB risk factors
      - Country of birth
    - CXR
    - No TST or IGRA
    - Treat if TB risk factors > risk of INH

Thorax. 2005 ;60(10):800-5

Screening LTBI

Summary of our recommended screening protocol

1. History for tuberculosis risk factors* from all patients
2. Interferon γ release assay: all patients
3. Chest x-ray: all patients, unless in low-risk group†

↓

Any of

1. Chest x-ray changes
2. Prior personal history of TB (inadequately treated or incompletely documented)
3. Positive Interferon γ release assay‡

YES → Refer for treatment of LTBI +/- further investigation

NO → No further screening§

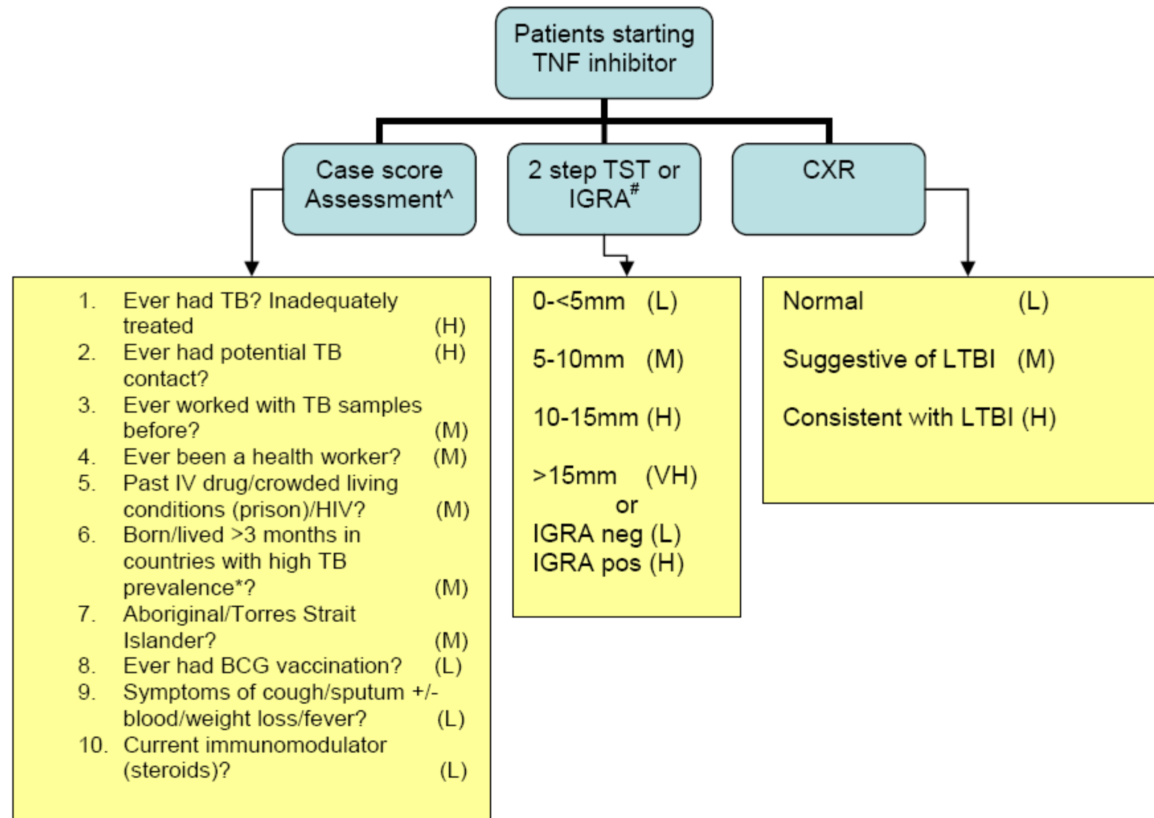
LTBI = latent tuberculosis infection. * Tuberculosis (TB) risk factors are history of birth or residence in a TB-endemic area, history of contact with active tuberculosis, or prior personal history of tuberculosis. † Low-risk group = Australian-born, younger than 50 years, with no TB risk factors. ‡ Indeterminate results: consider repeat test in 2 weeks if not immunosuppressed, or discuss with infectious diseases specialist. § If TB risk factors, maintain heightened vigilance for signs and symptoms of TB infection during tumour necrosis factor inhibitor therapy. Consider performing a Mantoux test as well to increase sensitivity. ◆

Med J Aust. 2008 ;188(3):168-70.

Screening LTBI

- Australian Rheumatology Association
  - Case history TB risk factor assessment AND
  - CXR AND
  - IGRA or Two step TST
  - If any “high risk” modality OR
  - If any multiple “moderate risk” modality refer for LTBI treatment

Screening LTBI



Australian Rheumatology Association Guidelines 2010

Screening effective?

- BIOBADASER patients
  - Rates of TB compared with:
    - Background Spanish population
      - 20.9 times higher
    - Those with RA not receiving anti-TNF
      - 6.2 times higher
    - Pre and Post official recommendations for screening
      - Abnormal CXR, TST ≥ 5mm, contact hx
      - Treated 9/12 INH
  - Reduction of between 79 to 83% in rates of active TB

Arthritis Rheum. 2005 Jun;52(6):1766-72

Screening effective?

- Same group
  - BIOBADASER patients
  - Complete vs. non complete compliance
  - Non compliant with screening recommendations
    - Associated with 7 times increased risk of TB

Arthritis Rheum. 2007 Jun 15;57(5):756-61.

Local experience

- Australian Rheumatology Association Database (ARAD)
  - National register of patients on biologics
    - Control patients (not on biologics)
  - Voluntary basis via rheumatologists
  - 6 monthly surveys of patients
  - Outcomes: medical, quality of life, responses to medication
  - No cases reported to the database of disseminated TB

Compliance

- Gastroenterologists
  - LTBI screening prior to anti-TNF
    - 38/44 “screened patients”
    - 41/43 asked about TB risk factors
      - 34/41 asked for CXR
    - 27/39 used IGRA (QFN-G)
    - 11/27 used TST

IMJ 2011;41(6):462-466

Alternatives

- Serial Testing
  - Repeat TST +/- IGRA whilst on anti-TNF
    - Detect positive conversion
      - Identify previous false negatives
    - Treat for LTBI when this occurs
  - Studies have shown a conversion rate of up to 30%
    - Park *et. al.*
      - Negative initial TST
      - Repeat TST and IGRA after at least 1 year of treatment
      - TST converted to positive 28/86 (32.6%)
        - Associated with duration of therapy
        - 1 subsequently developed miliary TB

J Rheumatol. 2009 Oct;36(10):2158-63

Alternatives

- Fuchs *et al.*
  - TST negative
  - Treated with anti-TNF at least 3 months
  - "True TST response" = increase of 6mm between 1st and 2nd TST
  - All patients with ≥5mm referred and received treatment
  - 8/40 (20%) had a true response

Clin Rheumatology 2009;28:167-172

Post LTBI Treatment

- Sichletidis *et al.*
  - Greece
  - Screened TST and CXR prior
  - Abnormal CXR, TST ≥10mm
    - Treated with chemoprophylaxis
    - INH 6/12, INH and rifampin 3/12
  - Anti-TNF 2/12 post chemoprophylaxis
  - 36 completed course
    - 7 presented with active TB (19.4%)

Int J Tub Lung Dis 2010;10:1127-1132

Position

- Prior to anti-TNF therapy
- Screening with:
  - Assessment of TB risk factors
  - CXR
  - IGRA (TST)
- If high risk Hx
  - Treat regardless of negative IGRA/TST unless risk of INH unacceptably high
  - High risk :
    - Partially treated TB
    - TB contact(s)

Position

- Country of birth:
  - Perform alternate test if initial test negative
  - During anti-TNF:
    - Close clinical monitoring
    - Serial IGRA (TST)

Summary

- 2 cases of disseminated TB in those previously screened negative on IGRA/CXR
- Screening guidelines
  - Treat for LTBI on basis of Hx
  - Serial TST +/- IGRA

The End

- Thoughts?
- Experiences?
- Questions?