A FRESH PAIR OF EYES….

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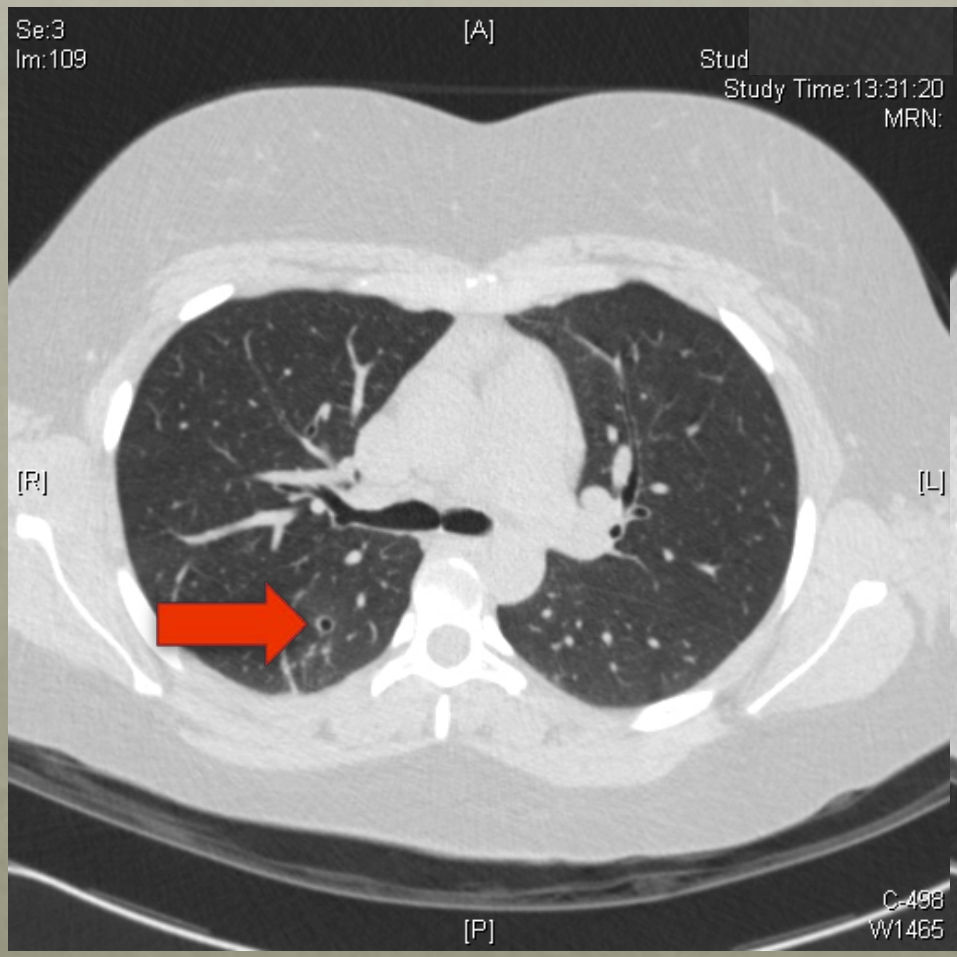
PAST HISTORY

- 24y female patient
- Atopy with eczema and hay fever
- Age 13 (2000) Episode of unexplained haemoptysis
  - Not investigated further as thought to be infection related
- Age 13 Left Achilles tendon contracture
- 2001 Tendon lengthening surgery
- 2002 Left Achilles tendon rupture
  - Biopsy shows a normal healing response secondary to rupture, no cause identified

REFERRAL 2003

- Smoker since her teens
- 2003 age 16 referred with recurrent small volume haemoptysis
- 2004 CT chest showed multiple pulmonary nodules with cavitation in the RML and both lower lobes
  - All tests including vasculitis and collagen vascular disease screens as well as sputum cultures normal apart from:
    - Raised IgE 3649 (<180)
    - Transient eosinophilia of 1.8 (0-0.4)
    - Ddimer 533 (<250)
    - Equivocal ANA
    - CRP 3 (0-6)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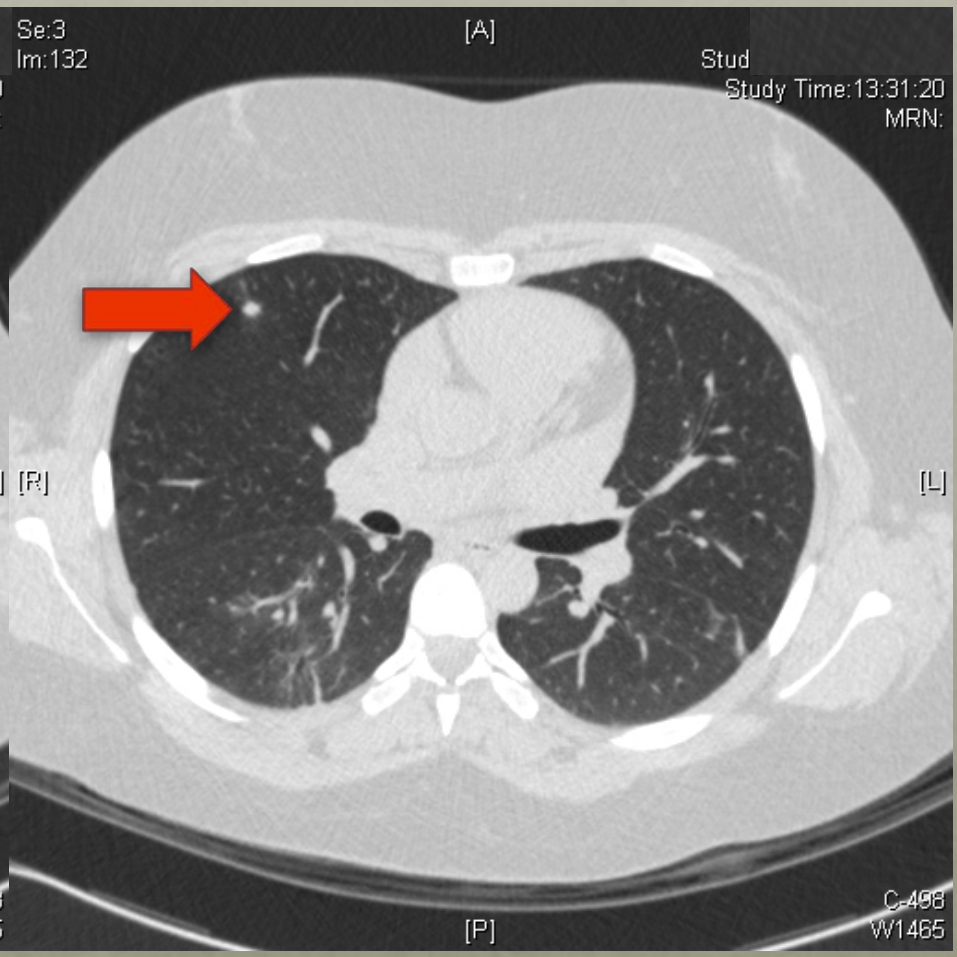
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INVESTIGATIONS

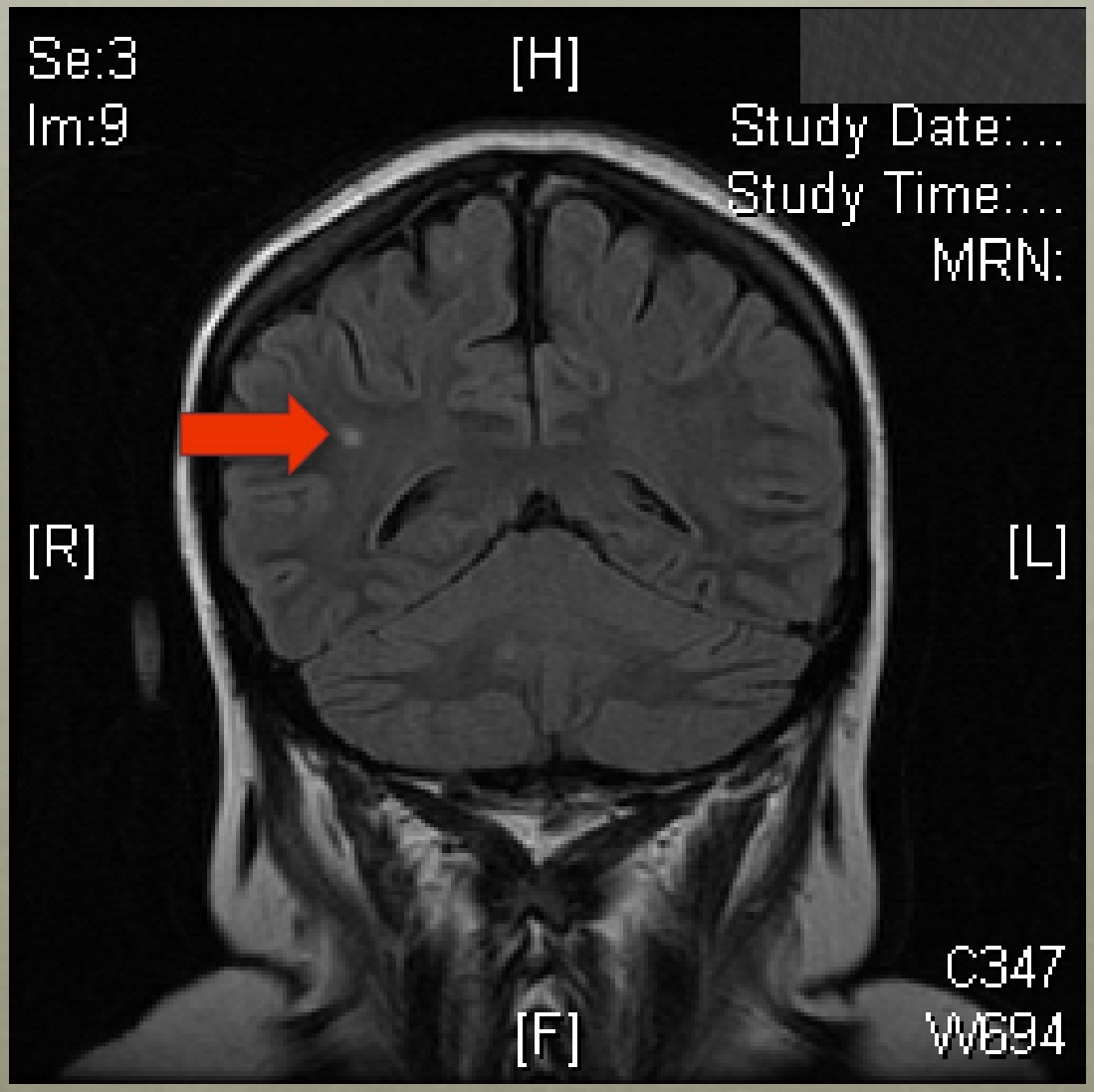
- Aspergillus Radioallergosorbent test (specific IgE) moderately positive, precipitating antibody negative
- Sputum culture and microscopy negative
- 11/2004 Video Assisted Thoracoscopic lung biopsy:
  - Non-diagnostic
- Bronchiolo-Alveolar Lavage: fungal culture negative but fungal hyphae seen – possible contaminant
- Treatment with Itraconazole initiated for Aspergillus
- Subsequent CT Chest 1/2005 showed cavitation largely resolved and GGO no longer seen

DIFFERENTIAL DX?

HISTORY CONTINUED

- Recurrent episodes of Left arm numbness followed by headache and photophobia
- Generalised seizure April 2005:
  - CT head normal
  - EEG normal
  - Bloods tests
    - TSH, FBC, LFT, Glucose, BFT all normal
    - Prolactin elevated
  - MRI head showed small 3mm T2 hyperintense, non-enhancing lesion R parietal white matter

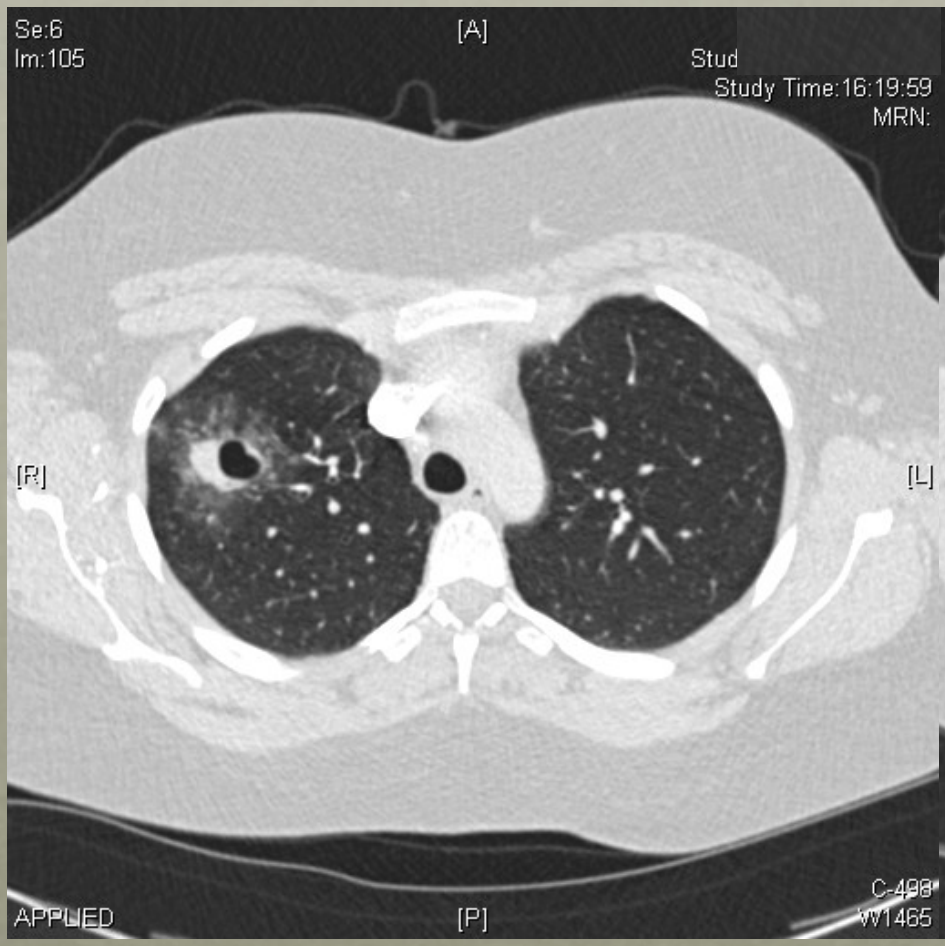
MRI



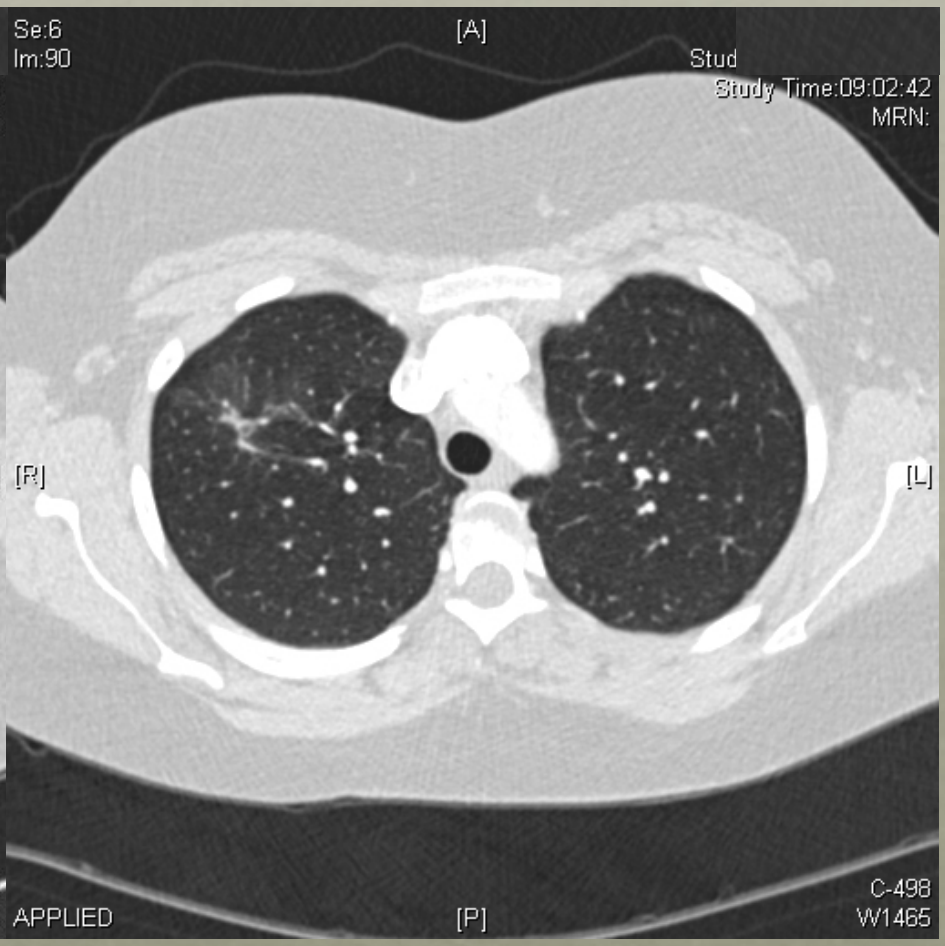
INVESTIGATIONS

- CT Chest: May 2005 – Recurrent multiple nodules (some cavitating) surrounded by ground-glass opacification. No mediastinal Lymphadenopathy
- CT Chest: October 2005 - Nodules resolved but progressive basal lung scarring, bronchiectasis and pleural thickening
- Blood tests all normal, Vasculitis screen, Immunoglobulins and functional antibody screen all normal
- Respiratory infection screen normal
- Itraconazole discontinued due to concerns over its effect on lowering seizure threshold

18/11/2005

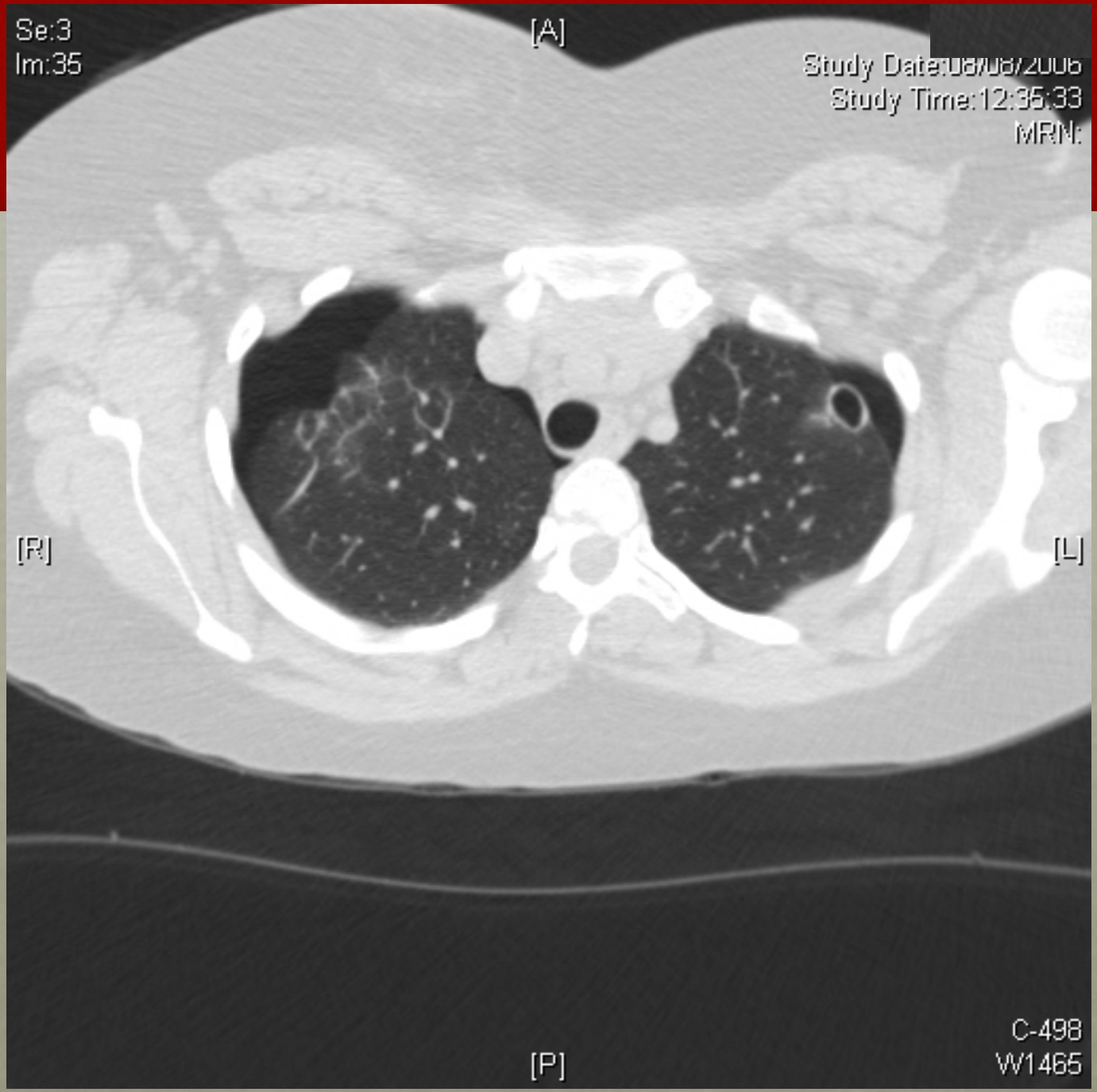


03/01/2006



HX

- Right Knee gave way July 2006 without preceding trauma
- Arthroscopy showed ACL deficient R knee
- Conservative treatment as L knee also showed ligamentous laxity
- Given Physiotherapy
- Eventually did have ACL repair in 2008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INVESTIGATIONS

- Blood tests all normal apart from falling MCV = 69 (81-96)
- Failed open lung biopsy due to respiratory arrest in theatre
- December 2006: Unwitnessed collapse with delayed recovery
  - MRI showed a small R parietal white matter lesion
  - EEG normal
  - Blood tests normal apart from a transiently elevated WBC count
- Prednisolone commenced February 2007
- Concerns regarding mental health prompted psychiatry referral
- CT Chest: October 2007 – much improved

SECOND OPINION

- Referred to The Brompton for a second opinion in December 2007
- CT Chest at The Brompton showed new cystic RUL and LUL lesions
- Noted:
  - retained primary teeth
  - hyper extensibility
  - past raised IgE/eosinophilia
- **Investigations:**
  - CRP 5, ESR 7 (<18)
  - IgE 165 (<180)
  - Normal: IgG, Alpha 1 AT, Serum electrophoresis, Complement, Thyroid function
  - Negative: Hepatitis serology, ANA, Aspergillus RAST, Lupus anti-coagulant, anti-cardiolipin antibody
  - Hb 11.3, renal function normal (incl 24h Unine protein)
  - Lung Function Tests: FEV1 120%, TLCO 84%, PO2 12.7 (Normal)
  - ECHO/Cardiac MRI both normal
  - No features of Churg-Strauss Syndrome
  - STAT 3 mutation testing requested

SECOND OPINION: OUTCOME

- **Royal Brompton 'disease features' list**:
  - Cavitating lung disease
  - Intermittent haemoptysis
  - Eosinophilia
  - Neurological symptoms
  - Hyper-extensible joints
  - Diagnosis: Hyper IgE syndrome (Job's Syndrome)
  - Plan: continue Prednisolone and DEXA scan

FURTHER DEVELOPMENTS

- Self poisoning attempt in April 2008 with opiate analgesic
- She discontinued her prednisolone in July 2008 and resumed smoking
  - All blood tests normal at that time including IgE
- In February 2009 she developed L hemiparesis associated with headache and vomiting
  - CT head showed a small R parietal white matter lesion (seen on MRI in 2007)
  - Blood tests all normal, CRP 4 (0-6)
  - Neurology opinion was more in keeping with hyperventilation than a generalised seizure
- August 2009: Admission under Infectious Diseases team for a witnessed generalised seizure complicated by aspiration pneumonia, haemoptysis and a L hemiparesis
  - Intubated 13-20/8/2009
  - Found to have Hashimoto thyroiditis with anti-thyroid peroxidase 2485
  - Blood cultures, LP, CSF PCR, Urine MC&S all failed to reveal a cause
  - Inflammatory markers in keeping with a pneumonia that resolved following antibiotics

I.M. PHYSICIANS LIST

- Review by Infectious Diseases consultant in clinic (September 2009)
  - Ligamentous laxity and tendon rupture without trauma and repeated L shoulder dislocations
  - Small joint hypermobility
  - Easy bruising
  - Thin skin
  - Spontaneous Pneumothoraces
  - Recurrent episodes of small volume haemoptysis
  - Cavitating nodules in lungs
  - Brain lesions and Epilepsy

SUGGESTIONS

- He suggested that the differential would include:
  - Vascular Ehlers Danlos Syndrome and
  - Langerhans Cell Histiocytosis
- Genetic referral made which also prompted
- Histology review of the original VATS biopsy sample from Papworth

Genetic Testing

- June 2010 seen by Clinical Genetics
  - Prominent veins
  - Scars from surgery slightly atrophic
  - No evidence of papery skin over elbows and knees
  - No stretchy or particularly smooth skin
  - Small but not large joint hyperextensibility
- Impression: Connective Tissue Disease possibly Vascular EDS but not typical
- Blood taken for COL3A1 gene testing

DIAGNOSIS

- Genetics and Histology consistent with vascular Ehlers-Danlos syndrome

- The pathology is the result of recurrent tearing due to lung fragility, with bleeding and repair with scarring.

VASCULAR EDS TYPE 4

- Autosomal dominant defect in type III collagen synthesis, penetrance nearly 100%
- Affects 1:100 000-250 000
- One of the more serious forms of EDS as vessels are prone to rupture
- Characteristic facial appearances:
  - Large eyes
  - Small chin
  - Thin nose and lips
  - Lobeless ears
- Small stature with slim build (patient was obese)
- Thin, pale, translucent skin
- 25% develop significant health problem by age to and 80% develop life-threatening complications by age 40 (retrospective analysis of 400 cases)
- Mean age of death 48y

QUESTIONS ?