

# A paradoxical paraparesis

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# Outline

- Case presentation of a severe, recurrent paradoxical reaction to tuberculosis, treated in a novel way
- What is a paradoxical reaction?
- What should I do about them?



# Presentation to MRI

# Presentation in July 2017

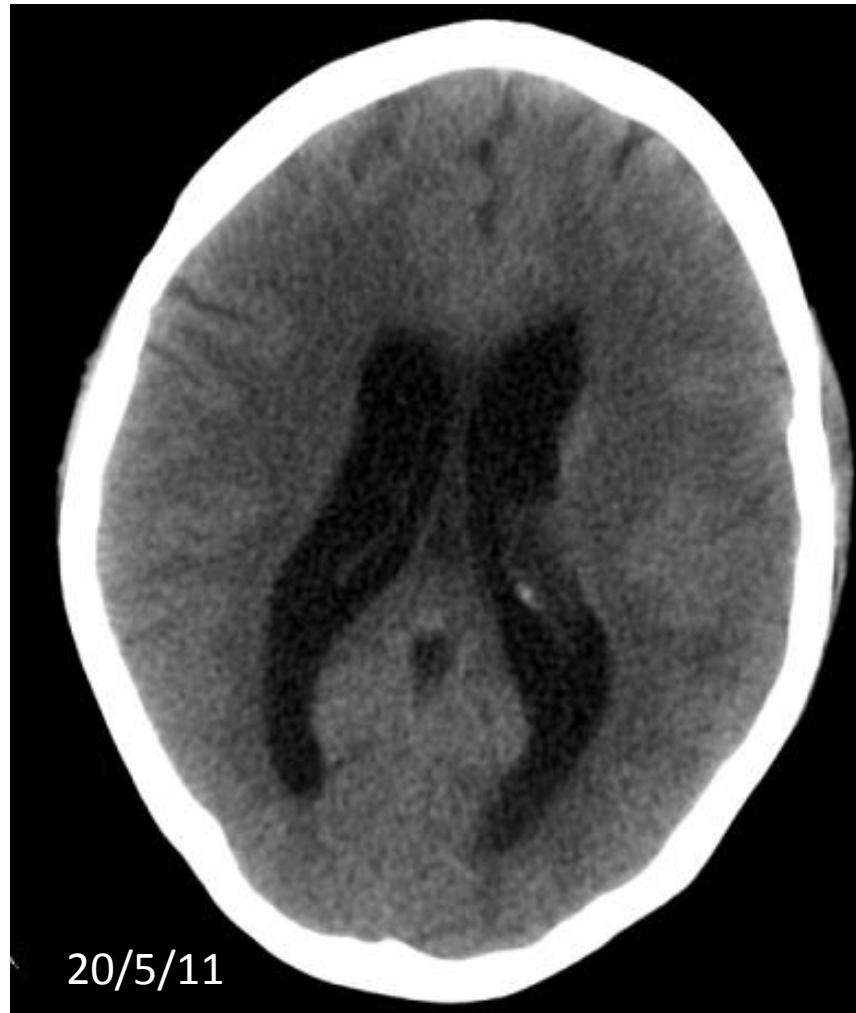
- 31y woman
  - New right lower limb weakness and difficulty passing urine – for previous ten days
  - No constitutional symptoms
  - On examination, spastic weakness of RLL (power 0/5)
  - Longstanding right III palsy and left hemiparesis
- 

The background is a solid dark red color. It features several large, semi-transparent geometric shapes in a slightly lighter shade of red. These include two large, stylized 'W' or 'M' shapes that are mirrored and positioned on the right side. On the left side, there are two circles of different sizes and a large, irregular polygonal shape. The word "Background" is written in a white, bold, sans-serif font, positioned in the middle-left area of the image.

**Background**

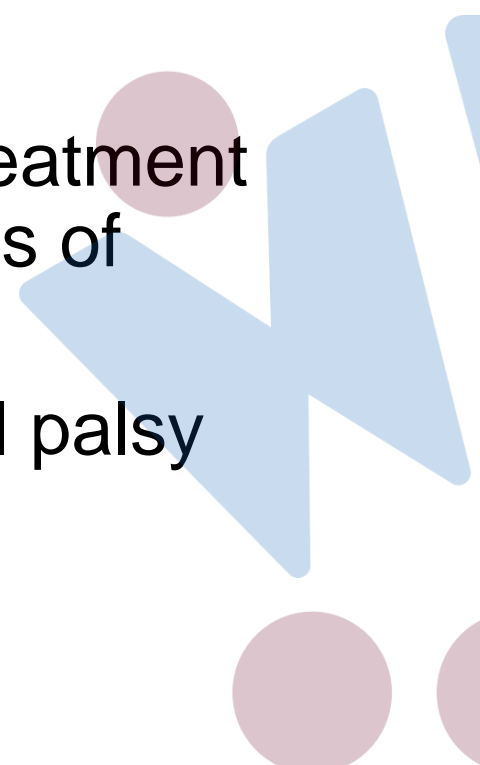
# First episode...

- Born in Somalia, HIV-negative
- Moved to UK 2009 (no subsequent travel)
- May 2011 – admitted from antenatal clinic at St Mary's Hospital with fevers and agitation

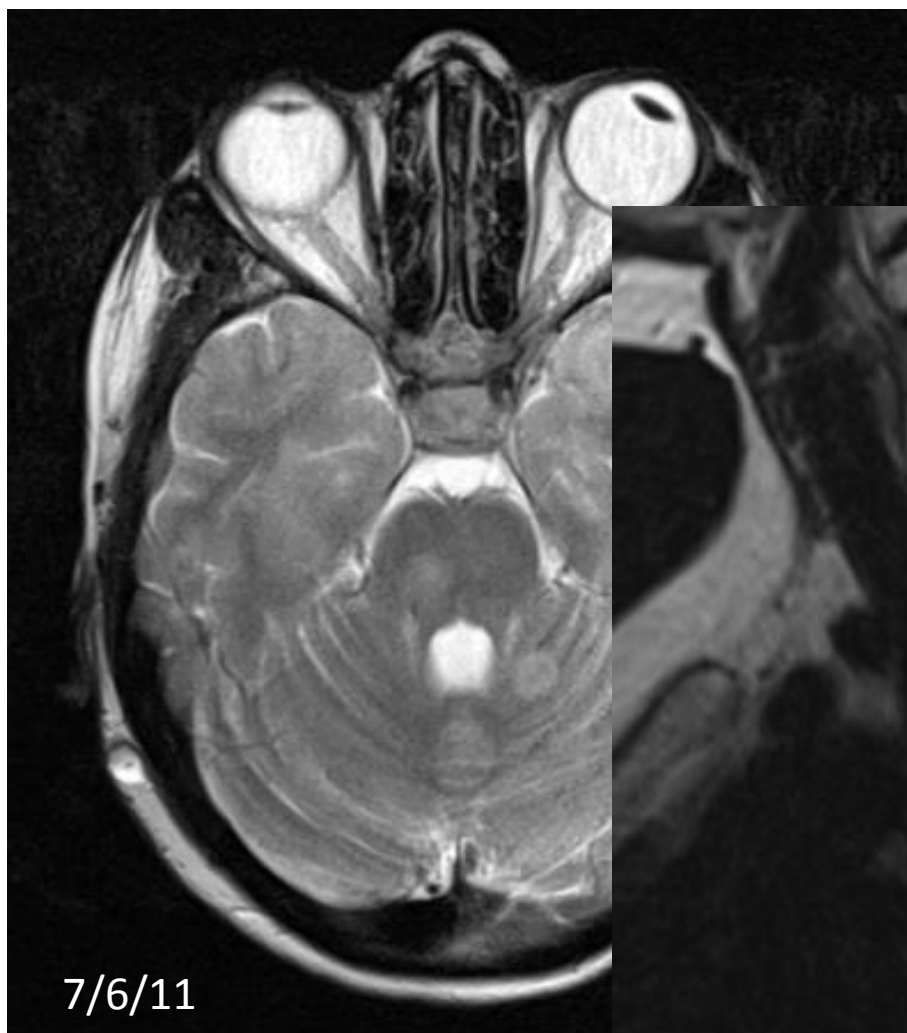


## First episode (2)

- Hydrocephalus, responded to intraventricular drain (later removed)
- CSF consistent with TB meningitis, treatment started with RHZE and reducing doses of dexamethasone
- Developed left hemiparesis and left III palsy

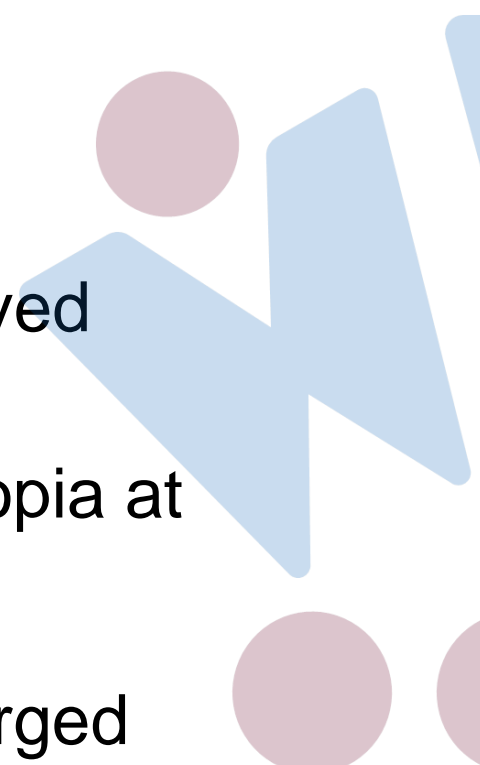






## First episode (3)

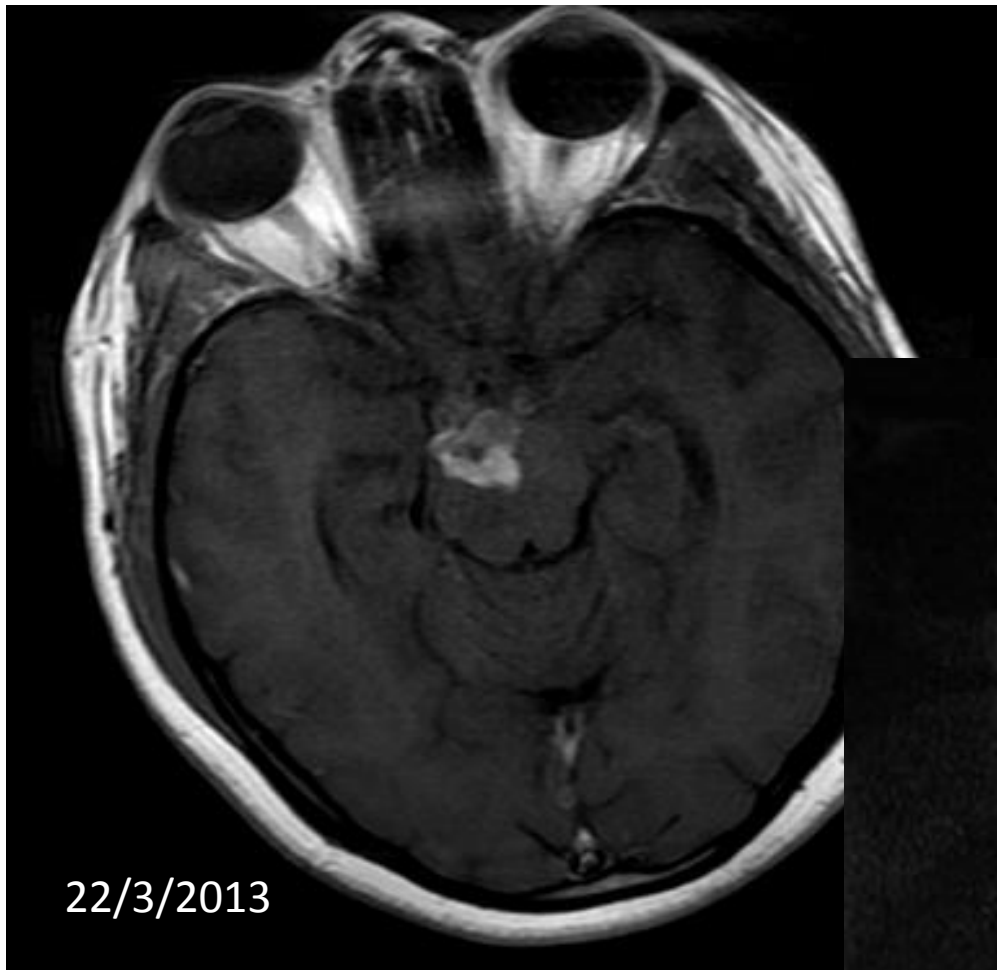
- Treatment complicated by drug-induced hepatitis – found to be due to pyrazinamide
- CSF grew fully-sensitive *M. tuberculosis*
- Treatment with RHE + dex continued
- Left-sided weakness and III palsy improved
- Weight increased dramatically
- Mild persistent left hemiparesis and diplopia at completion of treatment after 1 year, but functionally managing very well
- Remained well four months later, discharged from clinic




## Second episode (1)

- Headache since stopping TB treatment, progressive
- DNA'd MRI and admission for LP
- Admitted to local hospital with recurrence of symptoms with R III palsy March 2013
- Complex partial seizures
- Imaging showed multiple cerebral tuberculomata





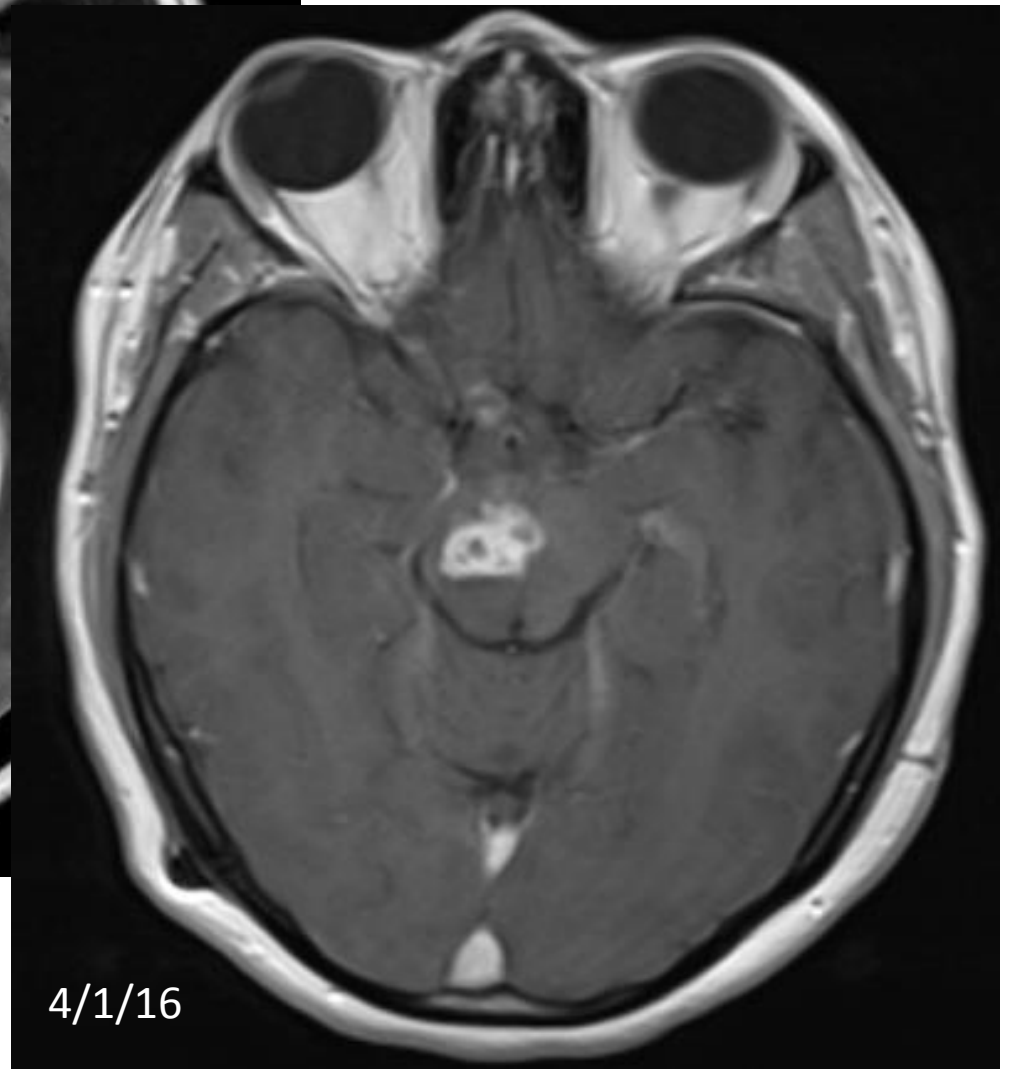
## Second episode (2)

- LP consistent with TBM (culture subsequently negative)
  - Treated at another hospital for MDR-TB plus RH (made harder by third pregnancy)
    - Plus dexamethasone
  - Headaches and vomiting recur whenever dexamethasone reduced
  - Symptoms worsened Sept 2015
  - Repeat MRI showed increasing size of tuberculoma above optic chiasm
  - Biopsy: caseating granulomata but TB culture negative
- 


## Second episode (3)

- Dexamethasone increased again
- BMI by this stage 43
- Headache repeatedly returned when dexamethasone weaned
- Eventually given infliximab and headache finally settled
- Took treatment for over 3 years in total





# Presentation in July 2017

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- 





# Treatment options

The background of the slide is a solid dark red color. It features a repeating pattern of abstract geometric shapes. These include circles of varying sizes and chevrons (V-shapes) of varying sizes, all rendered in a slightly lighter shade of red than the background, creating a subtle, textured effect.

# Third episode (2)

- What is this?
  - Recurrent/relapse drug-sensitive TB
  - Recurrent/relapse mega-resistant TB
  - Something else
  - Paradoxical reaction
- Need to sample CSF
- Unfortunately, after repeated LPs in 2013-15, LP became impossible



## Third episode (3)

- Treated initially with very high-dose steroid therapy
  - 1g methyl-prednisolone iv od for 5d
  - With bone and gastroprotection, infection prophylaxis
- Plan to continue weaning dexamethasone using Thwaites regimen
- She then refused all further steroids
  - Due to previous weight gain (and felt unwell taking them)



## Third episode (4)

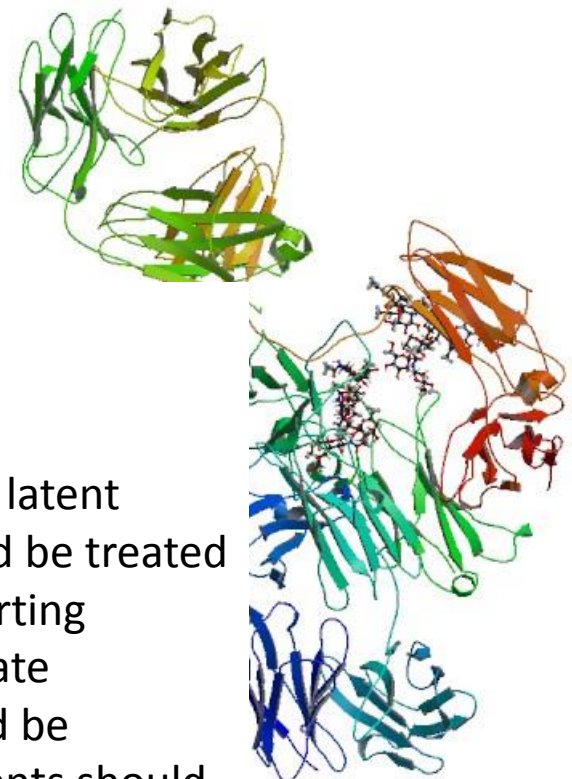
- Decision made to give her another course of infliximab

### BNF: Cautions, further information

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#### Tuberculosis

Manufacturer advises to evaluate patients for active and latent tuberculosis before treatment. Active tuberculosis should be treated with standard treatment for at least 2 months before starting infliximab. Patients who have previously received adequate treatment for tuberculosis can start infliximab but should be monitored every 3 months for possible recurrence...Patients should be advised to seek medical attention if symptoms suggestive of tuberculosis develop (e.g. persistent cough, weight loss and fever).



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# Third episode (5)

- High cost drug

Dear Dr Gorsuch

Your individual funding request for Infliximab (Remsima) for Paradoxical reaction to previous spinal tuberculosis, leading to paraparesis.

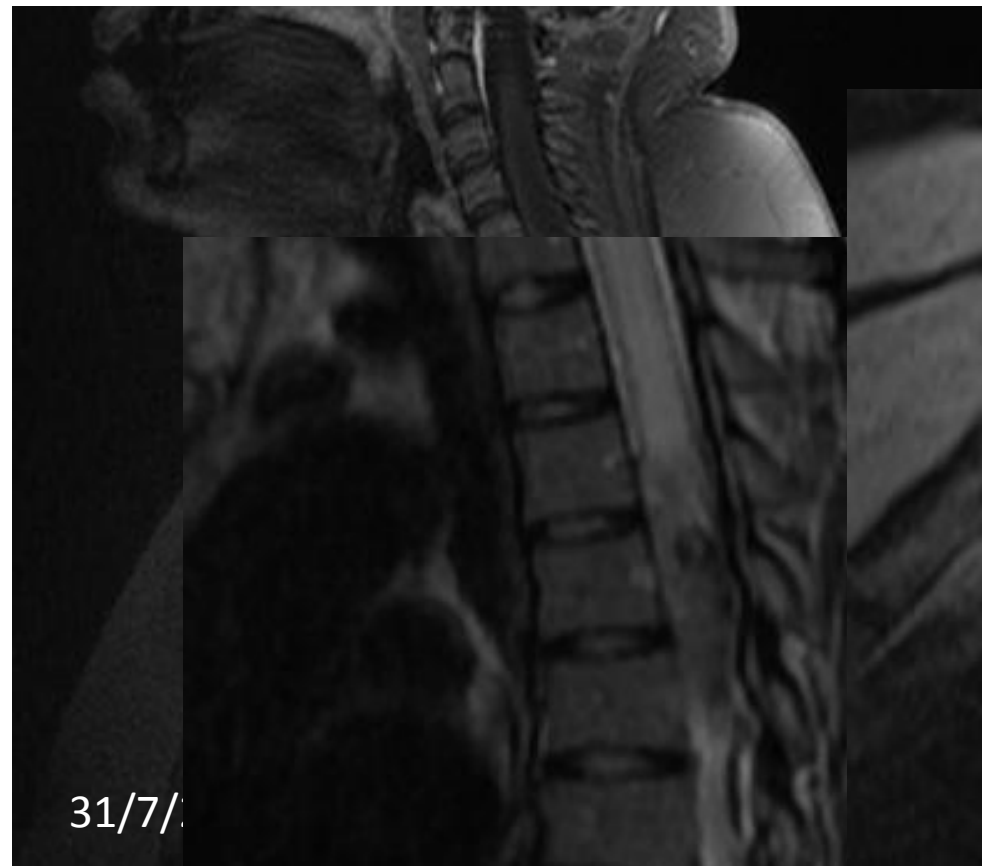
NHS NO: [REDACTED]

I am writing to inform you of the outcome of your Individual Funding Request (IFR) which was received on 04 October 2017 and considered by the IFR Screening Group on 17 November 2017.

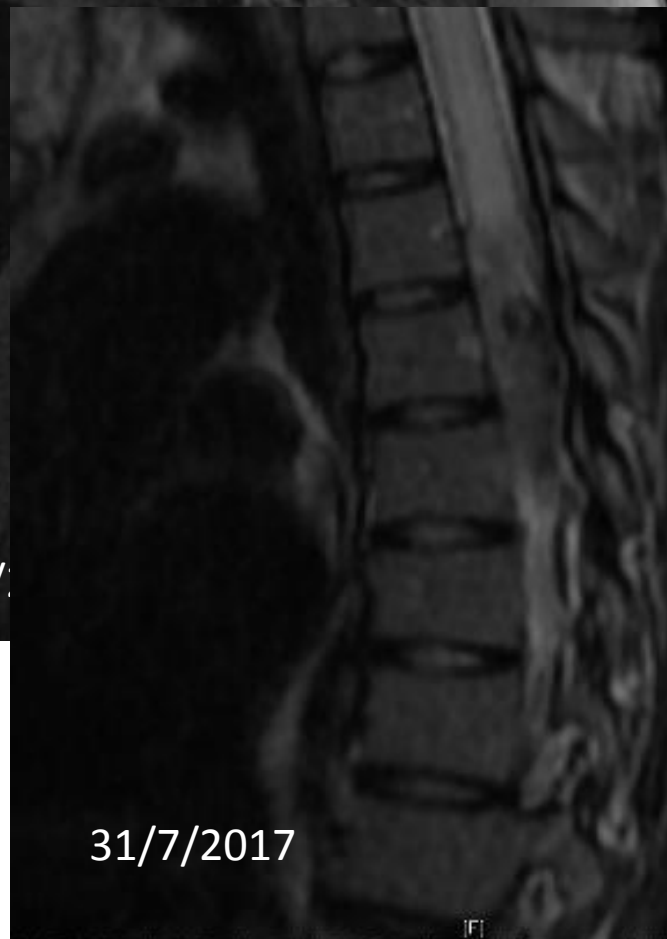
I regret to inform you that, the IFR Screening Group concluded that your request should not go forward for consideration by the IFR Panel, and are declining your request at this stage. This is because this patient is representative of a group of patients who have a similar condition and are at the same stage of that condition and who could potentially all request the same treatment. This makes it unlikely that [REDACTED] can demonstrate the necessary clinical exceptionality for an IFR to be successful.

The background is a solid dark red color. It features several faint, semi-transparent geometric shapes: circles and triangles. A large, stylized, semi-transparent 'W' shape is prominently displayed in the background, spanning across the middle and right side of the image. The text 'Response to therapy' is centered on the left side of the image.

**Response to therapy**



31/7/



31/7/2017



8/12/17



## Third episode (7)

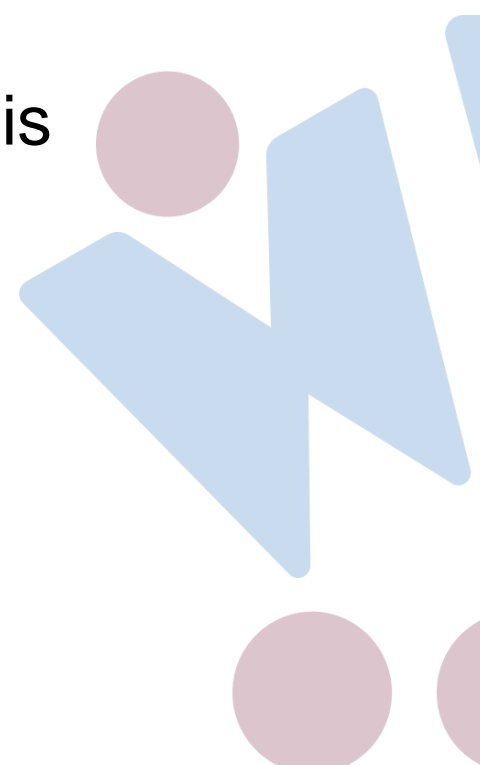
- Around the time of the second dose, showed signs of movement in RLL
- By time of discharge from neurorehab unit, had reasonable power in RLL
- Did not have significant functional improvement
- Home, but remains hoisted
- Has declined all subsequent hospital appointments and imaging



# Paradoxical reactions and IRIS

# What is paradoxical reaction (PR)?

- Transient worsening of inflammatory symptoms after initial improvement
- During (or after) treatment for tuberculosis
  - Worsening of existing symptoms
  - Development of new symptoms
    - Lymphadenopathy
    - Pleural effusion
    - Pulmonary
    - CNS
  - Fever
- After exclusion of other causes
  - Non-adherence
  - Resistance
  - Co-morbidity



# IRIS

- PR is seen in people with HIV on starting antiretroviral treatment
  - Usually known as Immune Reconstitution Inflammatory Syndrome (IRIS)
  - Can be paradoxical
    - worsening during or after treatment
  - Or “unmasking”
    - Development of symptoms for the first time shortly after starting ART
- Also rarely described on stopping anti-TNF biologics



# PR is common

- Data poor
- IRIS used to affect c. 25% of those starting ART
- Perhaps 25-40% have some evidence of PR
- PR significant enough to warrant treatment is uncommon, c. 5%
- PR bad enough to cause significant disease is rare

# Risk factors for PR/IRIS

- High mycobacterial burden
  - Smear-positivity of sputum and CSF (IRIS)
  - Disseminated disease
  - Urinary LAM (IRIS)
  - Low CD4 count (IRIS)/low lymphocyte count (PR)
- Inflammatory response
  - Single nucleotide polymorphisms in pro-inflammatory cytokines associated with IRIS
  - Rapid rise in CD4 count on initiation of ART
  - Starting ART soon after starting TB treatment



# Treatment of PR

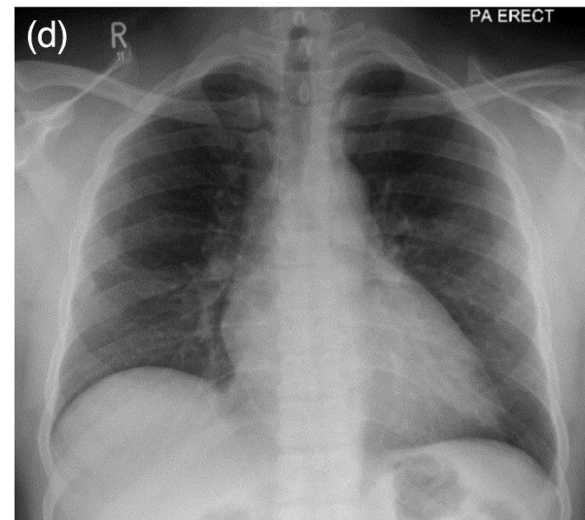
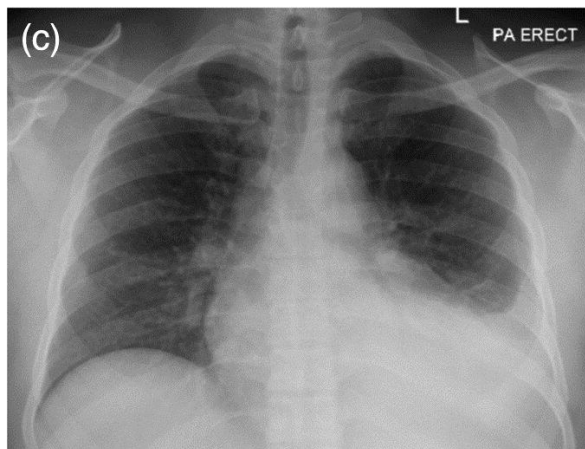
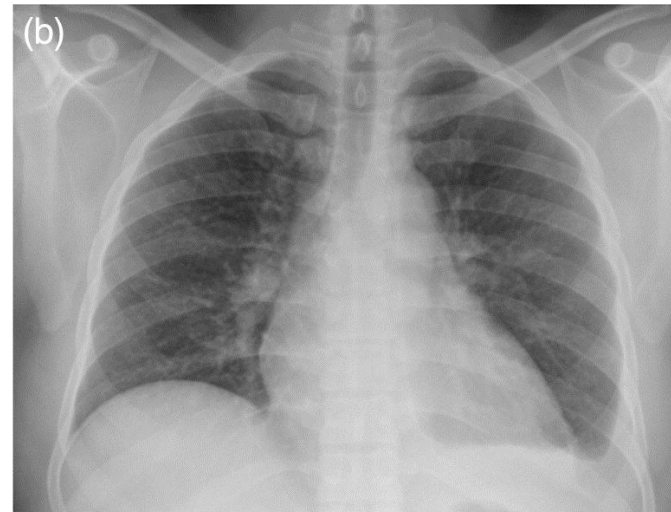
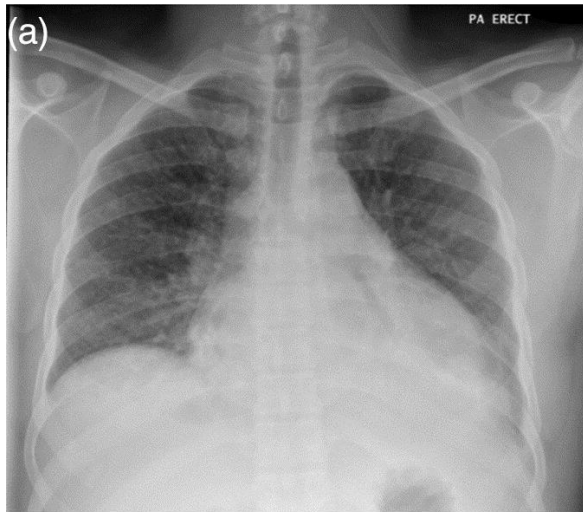
- Usually require no treatment
- Corticosteroids

- Lymph nodes: 60mg od initial (rifampicin)
- CNS: dexamethasone initially in divided doses

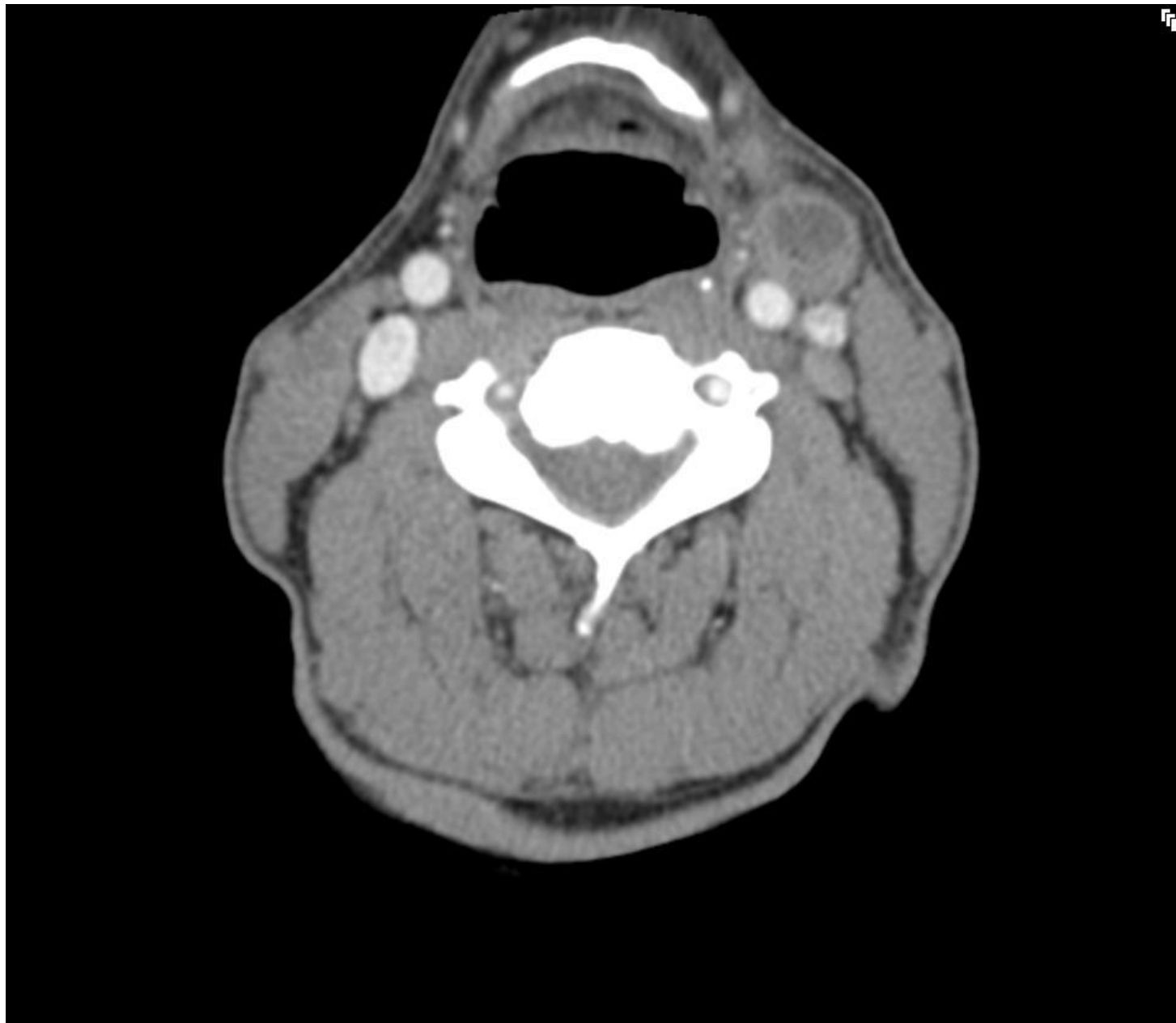
- Other immunomodulatory agents

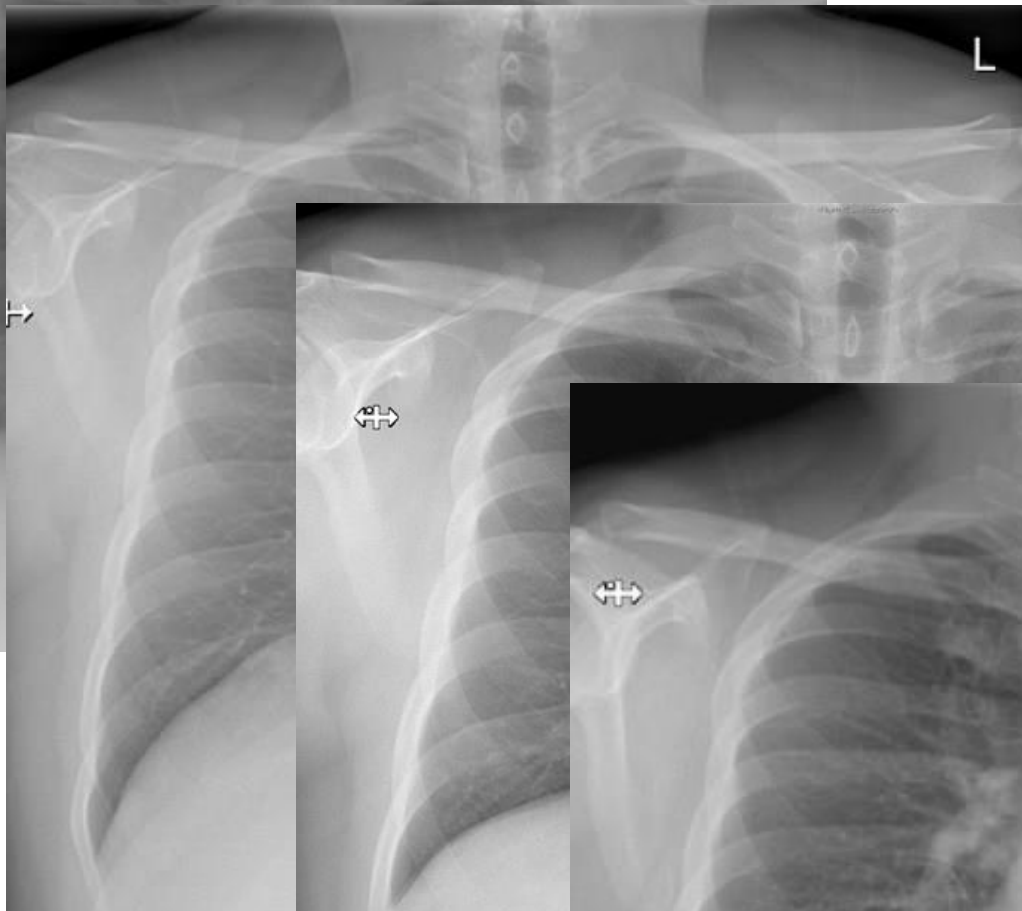
- Montelukast
- Thalidomide
- Anti-TNF biologics

	Stage <sup>a</sup>	
Dose of dexamethasone by week	1	2 or 3
1	0.3 mg/kg/day (IV)	0.4 mg/kg/day (IV)
2	0.2 mg/kg/day (IV)	0.3 mg/kg/day (IV)
3	0.1 mg/kg/day (oral)	0.2 mg/kg/day (IV)
4	3 mg/day (oral)	0.1 mg/kg/day (IV)
5	2 mg/day (oral)	4 mg/day (oral)
6	1 mg/day (oral)	3 mg/day (oral)
7	–	2 mg/day (oral)
8	–	1 mg/day (oral)



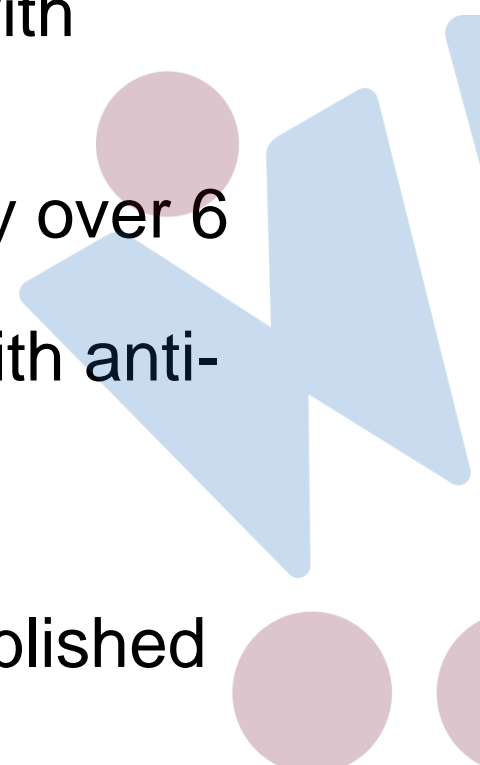






# Case summary

- This was a very complex case of CNS tuberculosis which left a young patient with severe disability
- Recurrent CNS symptoms were due to paradoxical reaction (possibly repeatedly over 6 years)
- Treatment for the second relapse was with anti-TNF agents alone, without TB treatment
- This led to clinical (but little functional) improvement
- No cases previously described in the published literature



# Any questions?

- Thanks to:
  - Christine Bell

