

Two types of immune driven deterioration

- Paradoxical TB-IRIS
 - Patients on treatment
- Unmasking TB-IRIS
 - Patients not on treatment

A definition of TB-IRIS

Case definition specific for tuberculosis-associated IRIS (Colebunders et al, 2006)

For patients receiving treatment for tuberculosis and starting ART:

Suspected tuberculosis-associated IRIS case

Cases must meet the following three criteria:

- An initial clinical response to tuberculosis treatment, based on a combination of some of the following factors: cessation of fever, relief of pulmonary symptoms, decrease in lymph node size, termination of signs of meningeal irritation (depending on presenting symptoms)
- New persistent fevers without another identifiable cause and/or one or more of the following: worsening or emergence of dyspnoea, stridor, an increase in lymph node size, development of abscesses, development of abdominal pain with ultrasound evidence of abdominal adenopathies, unexplained CNS symptoms
- Adequate adherence to ART and tuberculosis treatment

Confirmed tuberculosis-associated IRIS case

Cases must meet the following three criteria:

- Radiological examinations showing worsening or emergence of intrathoracic lymphadenopathy, pulmonary infiltrates, pleural effusions, abdominal lymph nodes, hepatosplenomegaly
- A good virological response and/or increase in CD4+ lymphocyte count, and/or conversion of tuberculin skin test from negative to positive, and/or adequate adherence to ART and tuberculosis treatment
- A clear exclusion of other conditions that could explain the clinical manifestations of the patient, such as tuberculosis treatment failure or other concomitant infections, tumours, or allergic reactions

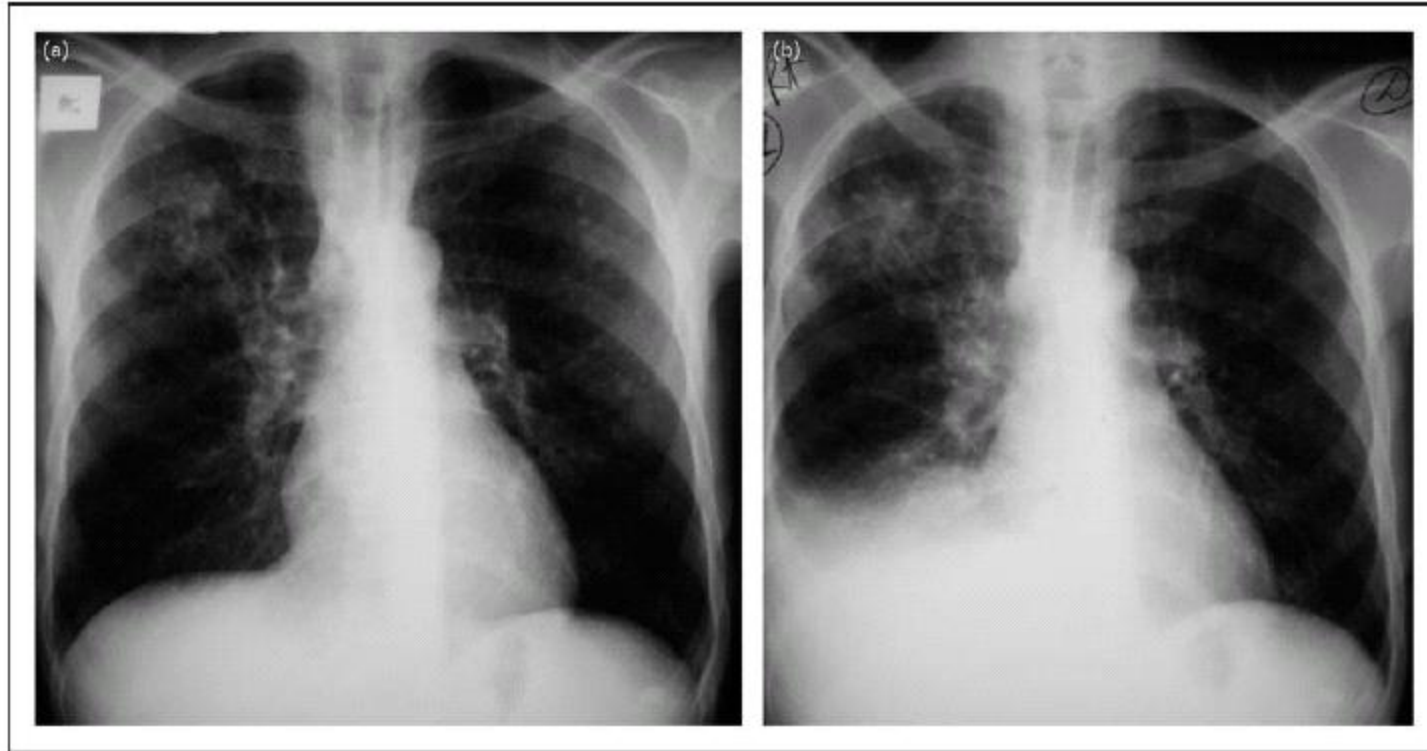
Paradoxical TB-IRIS is common but usually mild

Estimates of incidence range from 8-43%

Risk factors; low CD4 counts, high viral load, short interval between initiation of TB treatment and HAART

Low mortality (0-12%)

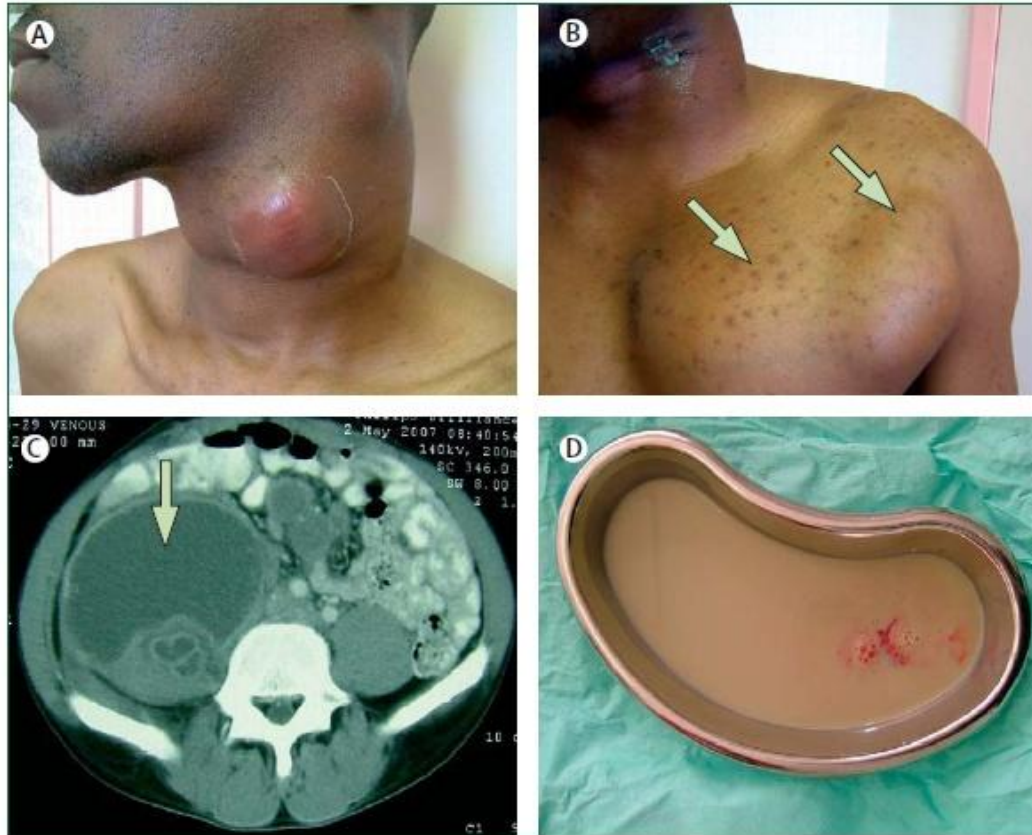
Pulmonary paradoxical TB-IRIS relatively common



Presentation

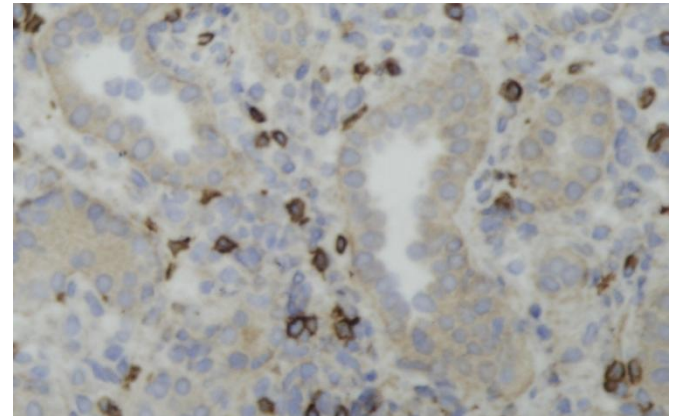
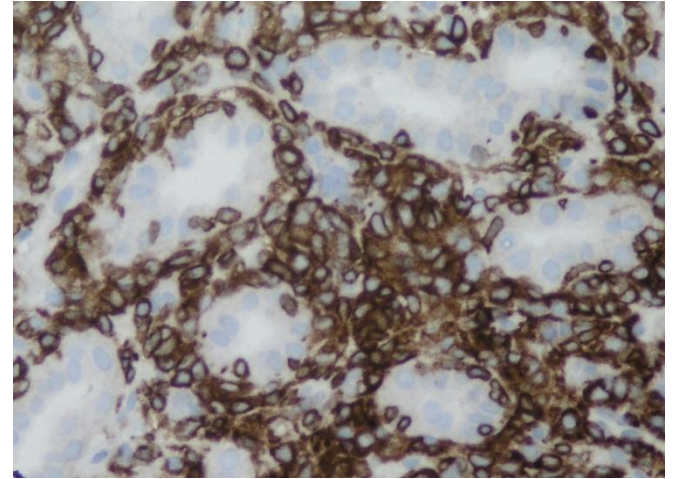
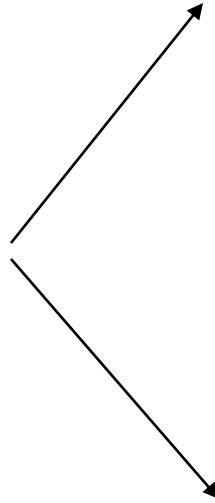
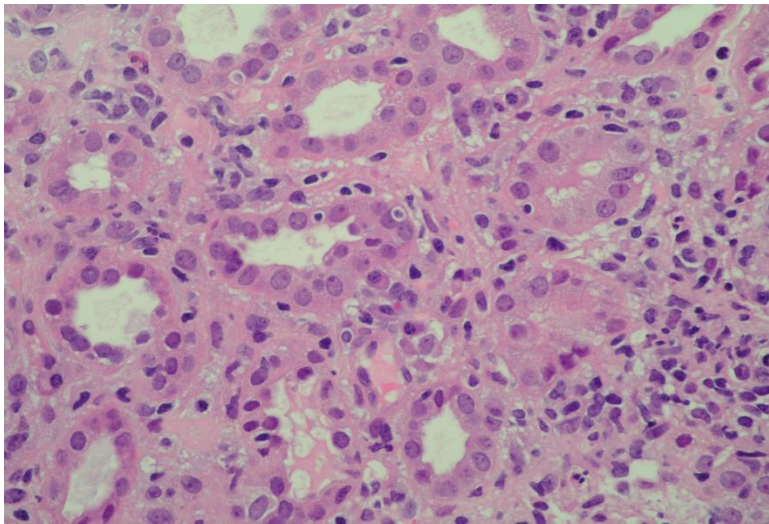
Week 4

Varying clinical manifestations in one patient



Neurological paradoxical TB-IRIS more of a challenge

But can have varied clinical manifestations



Treatment of paradoxical TB-IRIS

Evidence from SA RCT (Meintjes et al , CROI 2009) that prednisolone can reduce incidence of hospitalisation and drainage procedures

Local aspiration of site of infection may rapidly relieve symptoms

Unmasking TB-IRIS

Unmasking TB-IRIS typically within first 3 months of starting HAART

True incidence unknown; ethically hard to study

Potentially fatal

Treatment involves initiation of TB therapy

Diagnosing TB in immunosuppressed patient

Time since ART initiation (months)	Person time (years)	TB cases	TB incidence rate (per 100 person years)	95% confidence interval
0-3	138.00	24	17.39	11.65-25.94
3-6	130.65	11	8.42	4.66-15.20
6-9	126.44	7	5.53	2.64-11.61
9-12	122.67	7	5.71	2.72-11.97
12-18	236.84	13	5.48	3.18-9.45
18-24	214.20	8	3.73	1.87-7.47
>24	206.34	11	5.33	2.95-9.63
Overall	1175.17	81	6.89	5.54-8.57

A definition of unmasking TB-IRIS

Unmasking tuberculosis-associated IRIS (provisional)

We propose that the following could suggest a diagnosis of unmasking tuberculosis-associated IRIS:

- Patient is not receiving treatment for tuberculosis when ART is initiated and then presents with active tuberculosis within 3 months of starting ART

AND one of the following criteria must be met:

- Heightened intensity of clinical manifestations, particularly if there is evidence of a marked inflammatory component to the presentation. Examples include tuberculosis lymphadenitis or tuberculosis abscesses with prominent acute inflammatory features, presentation with pulmonary tuberculosis that is complicated by respiratory failure due to adult respiratory distress syndrome, and those who present with a marked systemic inflammatory syndrome related to tuberculosis. See example in figure 2
- Once established on tuberculosis treatment, a clinical course that is complicated by a paradoxical reaction