# Tuberculosis/HIV infection

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# HIV and TB

- **TB is the most common opportunistic infection in HIV infection and the first cause of mortality in HIV infected (10-30%)**

- **10 millions patients co infected in the world.**
  *11% in children ( 85% in SubSaharan Africa )*

- **Immunosuppression induced by HIV modifies the clinical presentation of TB :**

1. Subnormal clinical and roentgen presentation
2. High rate of MDR/XDR
3. High rate of treatment failure and relapse (5% *vs* < 1% in HIV - *)*

# Case 1

- A 33 year old woman, Ukraine origin

- **Presenting symptoms:**

1. Fever 39°-40° 1 month
2. Dry cough- abdominal pain

- **In the past:**

1. 10 years ago:“ pleuritis” , pleural punction
2. Intra venous drug addict
3. HIV test negative 6 years ago

- **Physical examination:**

1. Febrile , left pulmonary ronchus
2. Enlarged liver firm, non tender (7cm below the Rt costal margin )

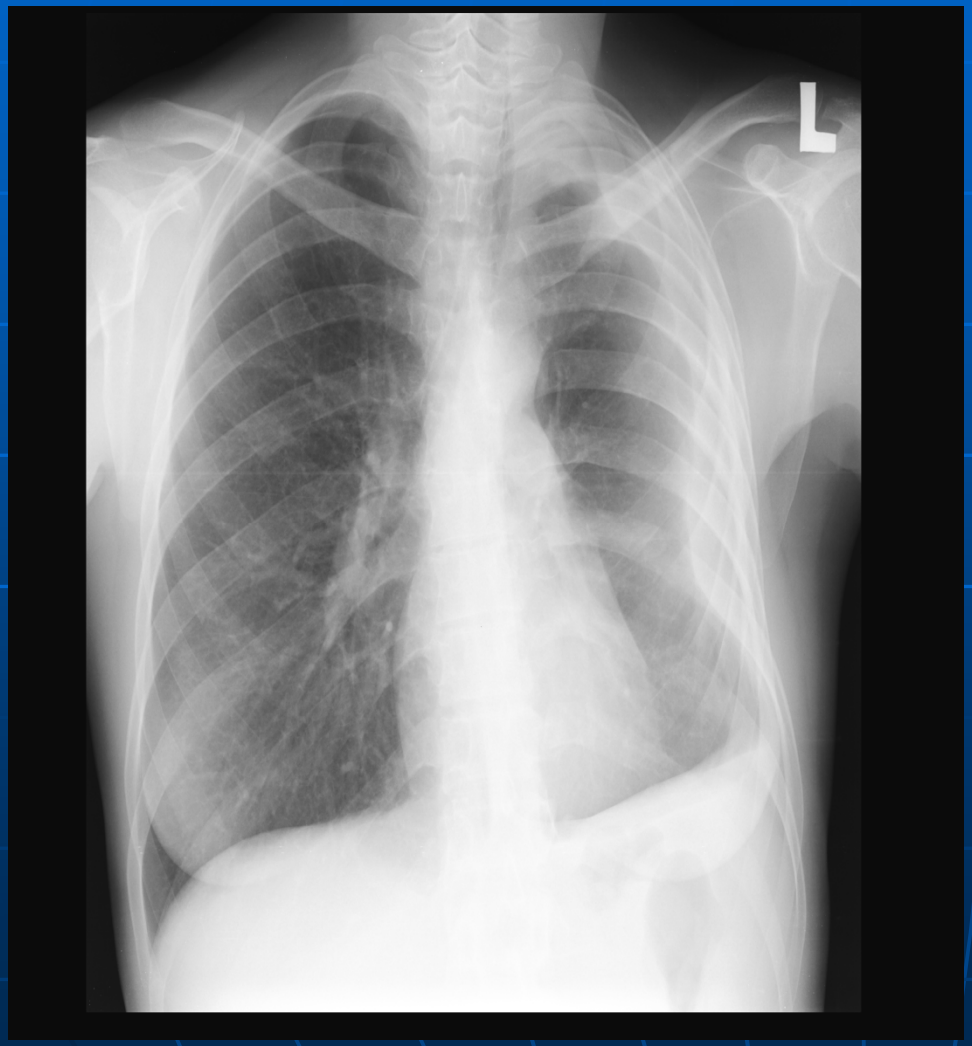
# Laboratory Results

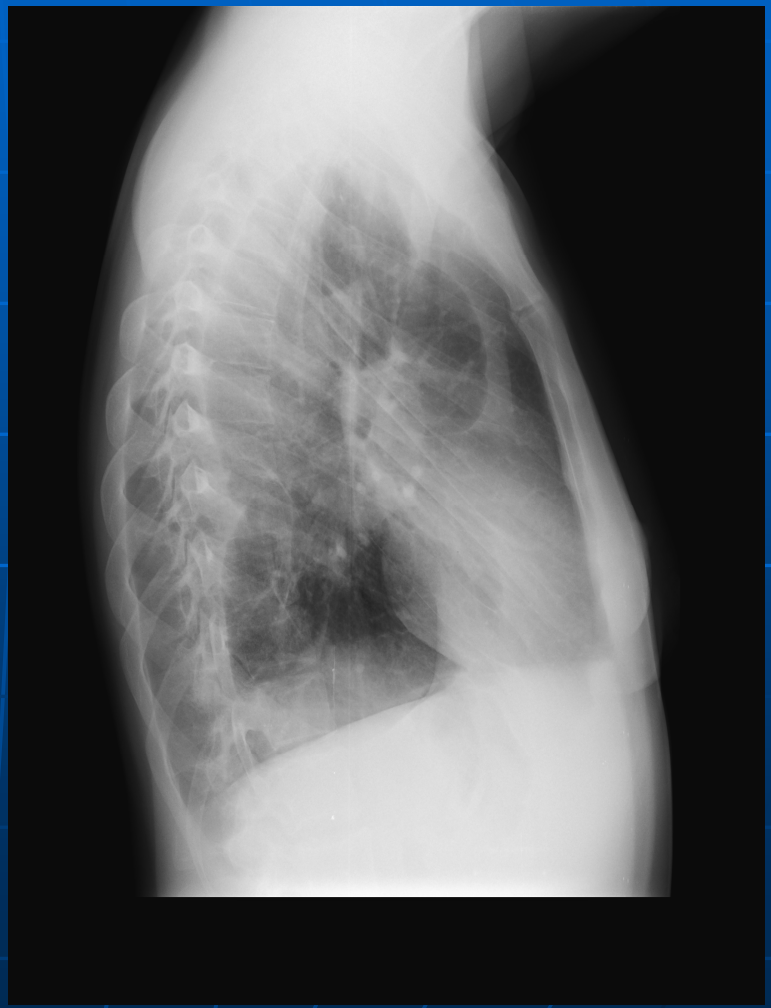
| ESR | Hb | WBC | PMN | LY | PLT |
|---|---|---|---|---|---|
| 140 | 9 g/dl | 7200<br>$10^3/\mu L$ | 81 % | 7% | 291.000<br>$10^3/\mu L$ |

| Natrium | Potassium | Urea | Creatinine | Protein | Albumin |
|---|---|---|---|---|---|
| 131 meq/L<br>(135-145) | 3.8 meq/L<br>(3.5—5.1) | 29 mg<br>(10-45) | 0.6 mg<br>(0.7-1.2) | 6.9 gr<br>(6-8) | 2.9gr<br>(3.5-5.5) |

| Alkal Phosph | γ GT | SGOT | SGPT | Bilirubine | PT-PTT |
|---|---|---|---|---|---|
| 1980 IU<br>(100-290) | 1138 IU | 42 IU<br>(11-39) | 78 IU<br>(9-37) | 1 mg | N |

# Case 1



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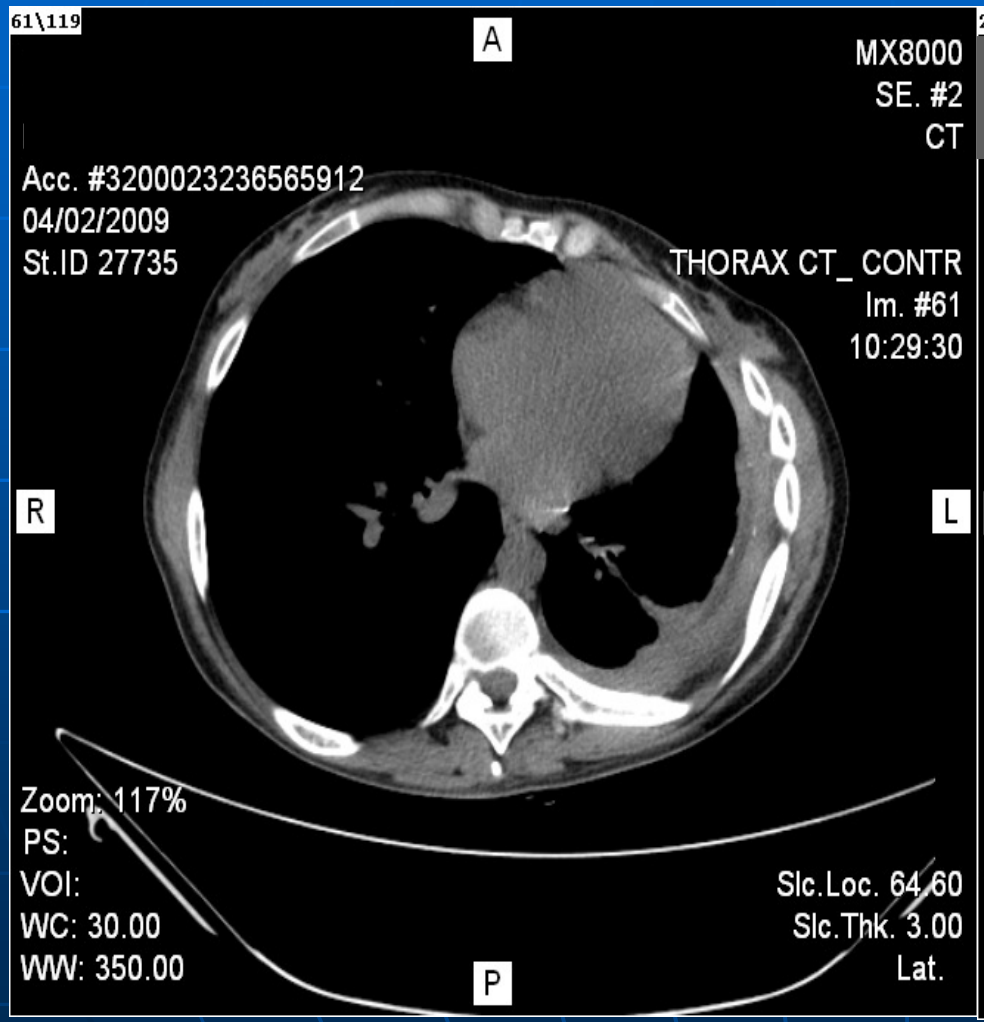
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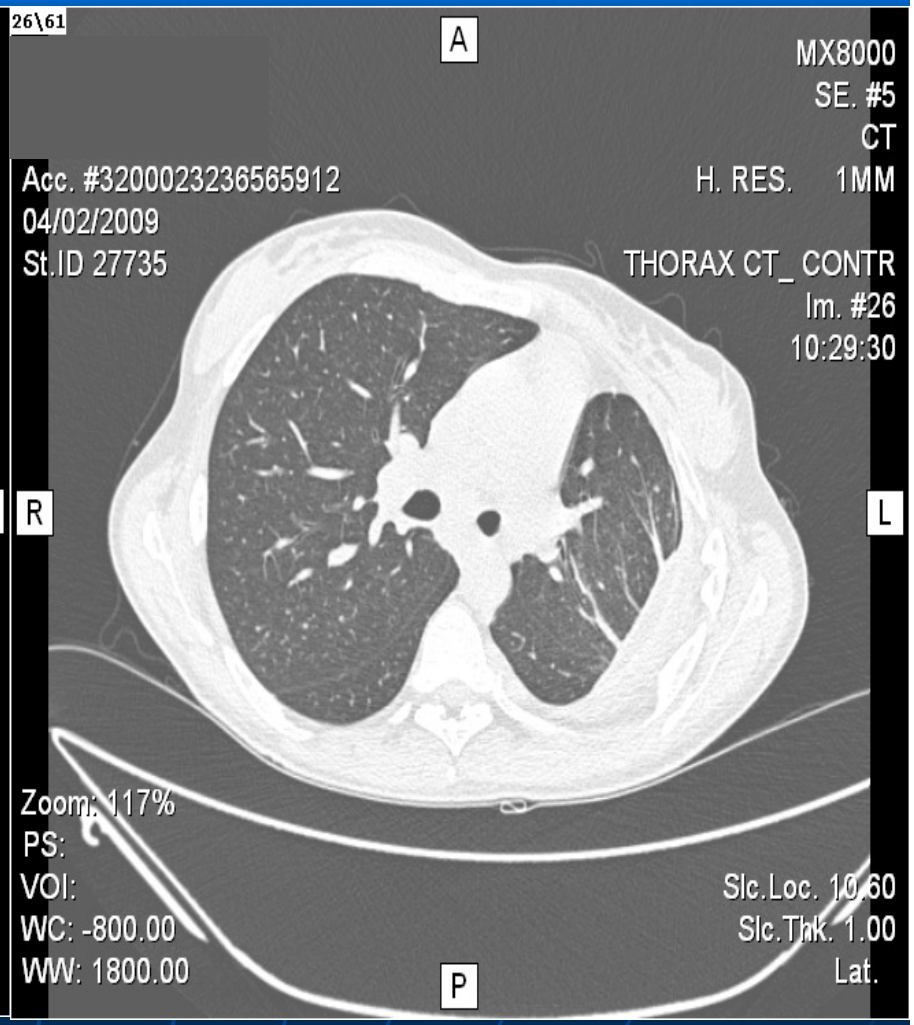
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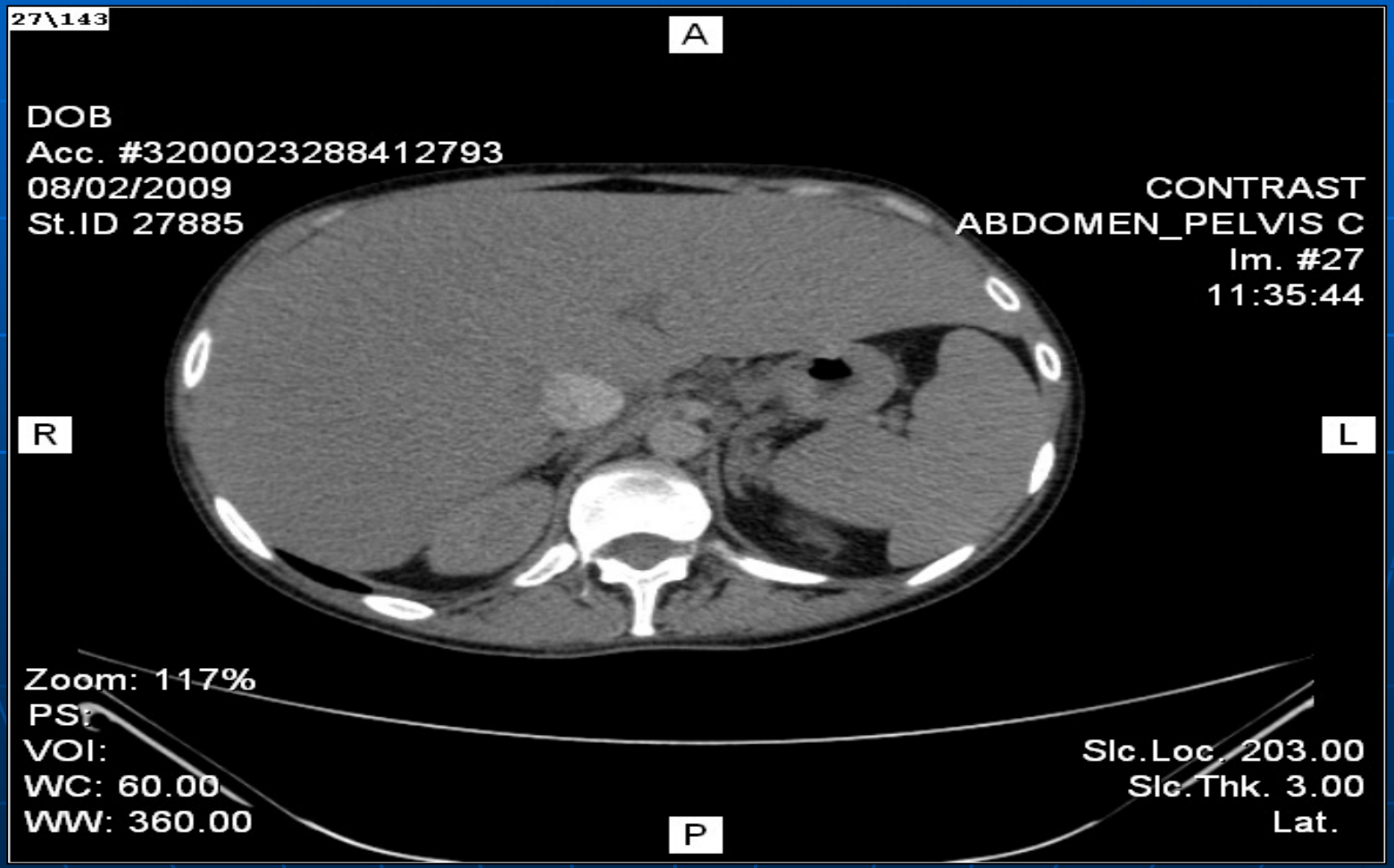
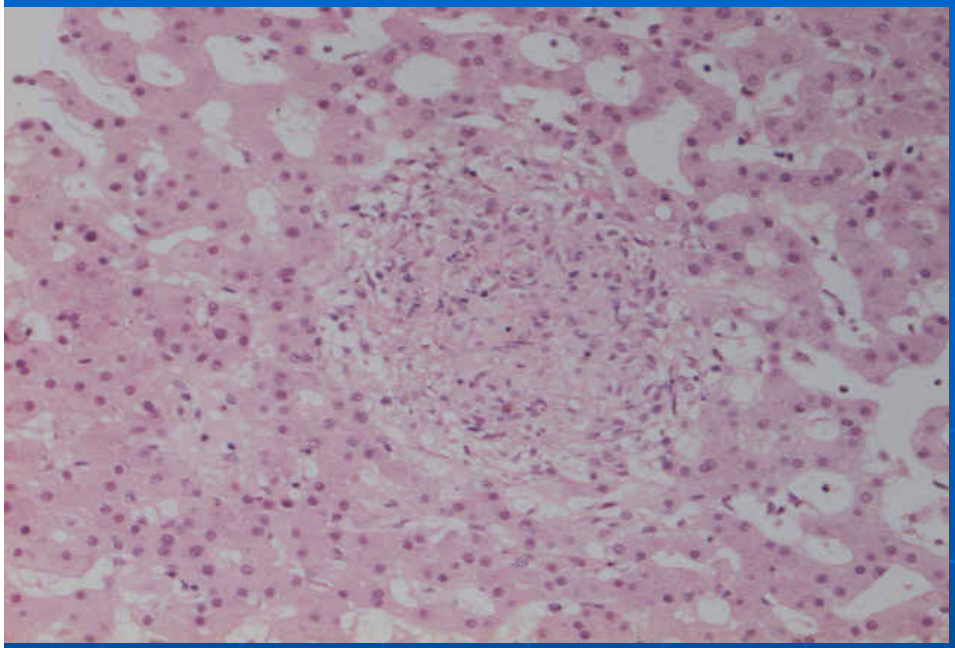
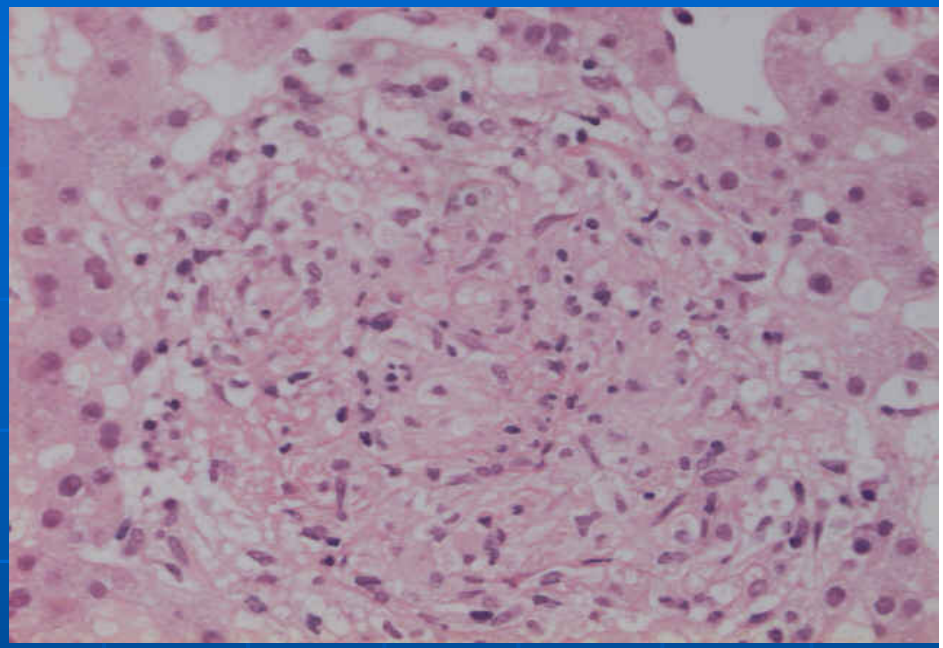
# Case 1

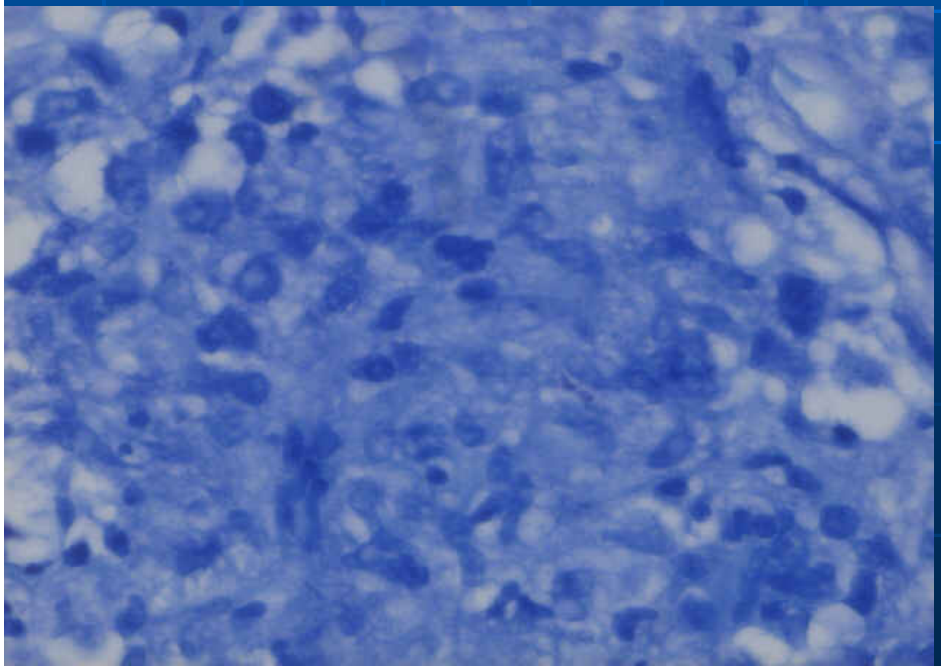
**Abdominal CT : *diffuse hepatic infiltration***

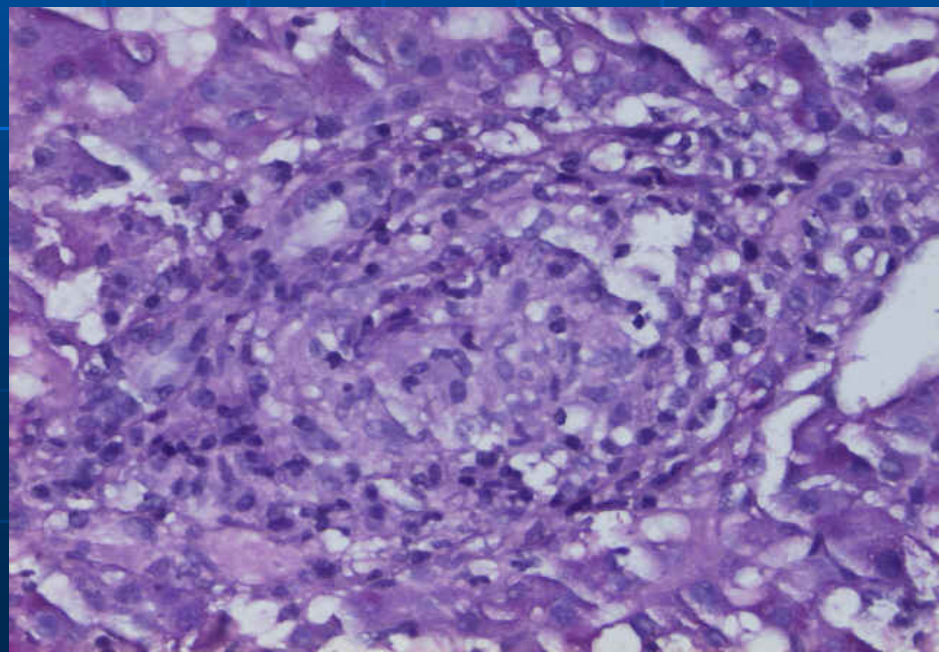


# Needle Core Biopsy: granulomas hepatitis









# Case 1

| HIV (Elisa +WB) | CD4 Cells / µL | VL | HBs Ag | HCV Ab | VDRL IGg | Blood culture | Sputum |
|---|---|---|---|---|---|---|---|
| + | 495 (15%) | >100.000 | negative | + | + | negative | AFB+Gene probe: negative |

***Liver granuloma and FUO in HIV positive patient***

***??????***

# Granulomatous Hepatitis: *2-15% liver Bx*

*Uta Drebber et al. liver international 2008: 828-834*

*Gaya DR et al. J Clin Patho 2003: 850-3*

*Dourakis SP et al. Euro J Gastroentrology Hepatol 2007:101-106*

| | **German** 442/12161 | **Greece** 66/1768 | **N Ireland** 63/1662 | **Saudi Arabia** |
|---|---|---|---|---|
| **Primary Biliary Cirrhosis** | **48.6%** | **68%** | **23%** | |
| **Sarcoidosis** | 8.3% | 7.6% | 11% | |
| **infectious** | **3.9%** **TB: 3cases** | | 4.8% | **55/59** **TB:19 cases** |
| **Chronic HCV** | | 7.5% | 9.5% | |
| **Drugs** | 2.4% | | 9.5% | |
| **Other** | 36% | | | |

# HIV and Hepatic Granuloma

- Literature : *Tb responsible for most of the cases*

1. ***retrospective study 1985-1997***

   ***Evaluate etiology 93 pts with HIV, FUO and HG .***
   ***TB responsable for all the cases (78%with other site TB)***

1. ***Liver specimen obtained from 171pts with AIDS***

   ***Significant microscopic abnormalities in 58%***
   ***70 pts with TB (35 with anatomical TB lesions***

*Vidal F et al . Int Conf AIDS 1998 12:288*
*Lanjewar DN . HIV 2004:253-7*

- Hepatic tuberculosis is associated with 90% cases of miliary TB

- Tubercule bacilli reach the liver by way of hematogenous dissemination: Hepatic artery in case of miliary tuberculosis
  Portal vein in case of focal liver tuberculosis

# Case 1

- Antituberculosis treatment (INH, RFP, PZA ETB) progressive elevated doses
- Fever decreased dramatically and abdominal pain improved
- Progressive improvement in liver function
  (*Alk phosph decreased from 1980 IU to 200 IU )*
- Positive Tuberculosis Cultures : sputum and urine
- Non Caseiting granuloma in liver
- **Dg : Generalized Tuberculosis and AIDS (reactivation of old untreated TB)**

# Tuberculosis Treatment and HAART

- **Active TB is an AIDS-defining disease**

- **Begin anti TB treatment immediately**
  **Duration of Anti TB treatment** 9 months to 1 year

- **HAART Timing** : no consensus
  >200 cells/mm : defer until complete TB treatment
  >50 cells/mm and < 200 cells/mm: wait until induction phase
  < 50 cells/mm : start as soon as possible

- **Problems**:
  Drug toxicities (skin rash, hepatotoxicity)
  Drug interaction RFP decreases level of ARV drug- resistance
  Immune restoration induced by HAART may be associated with IRIS

**Use of HAART results in marked decreases of death and other opportunistic infection**

# Anti Retroviral Treatment

- A retrospective series from England :
- 188 patients：85% no antiretroviral-therapy when TB was diagnosed
  45% began HIV therapy during TB treatment
  (median of 2 months after TB diagnosis).
- 3.5%: new AIDS-defining illnesses (*compared with 24% in those not treated).*
- 50% Adverse Events (. peripheral neuropathy, rash, hepatitis, and GI)
- 30% either changed or interrupted TB or HIV treatment.
- **16 coinfected patients who died did not receive antiretrovirals**

*Dean GL et al. AIDS. 2002;16:75-83*

# Anti Retroviral treatment

- **Reverse Transcriptase inhibitor** :

  *interferes with the reverse transcription that converts HIV RNA to HIV DNA*

1. NRTI nucleoside analogue (AZT, lamivudine)
2. NNRTI non nucleoside analogue . (Nevirapine )

- **Pi: Protease Inhibitor**

  *prevents maturation of virion capable of infecting other cells*

  ( Indinavir, Ritonavir)

- **Treatment combination** (HAART)

  *2NRTI AND NNRTI . (EFV or NVP)1st line*

  *3 NRTI -alternative 1st line*

  *2NRTI and PIr (SQV/r or LPV/r and RTV – 2nd line*

- *Since the use of HAART, mortality from HIV has declined dramatically in the developed world.*

# HAART and TB : PROBLEMS

- **Toxicities:**

  14-20% of HIV+ pts starting ARV have elevation in Liver function tests
  2-10% need to interrupt ART because of significant hepatotoxicity
  CNS (EFV)
  Skin rash (NVR)

- **Drug interaction**:

  Regimen including Rifampicin reduce the therapeutic activity of NNRTI and PI through the cytochrome P450 enzyme
  Lead to HIV resistance

  *WHO recommendation: regimen containing EFV (2NRTI AND NNRTI )*

- **Immune reconstitution syndrome (IRIS)**

1. TB IRIS is characterized by clinical worsening soon after initiation of ART
2. Occurs in **10-30%** of patients commencing ART
3. Cause: recovery of the immune system after HAART institution with reconstitution of antigen-specific T cell-mediated immunity

*Important to differentiate from treatment failure*

# Case 1

- After 2 months of anti TB treatment, new test for CD4 :
  we begun on HAART (*CD4 fall from 495 to 35 cells/ µL)*
- No hepatotoxicity, Mild gastrointestinal troubles
- Few weeks after ARV treatment:
  Fever 39
  Blood culture negative
  Xray : no change
- IRIS  Steroid treatment for 1 month: improvement
- The pt is ongoing with both treatment

# Conclusion (Case 1)

- In HIV positive patient with fever, liver infiltration and Hepatic Granuloma, *Tuberculosis infection is highly suspected*
- *Anti TB treatment should be institute rapidly* as the diagnosis may be delayed
- *Actually, HAART and anti TB is safe* and reduces mortality especially if EFV regimen used
- *IRIS is* frequent

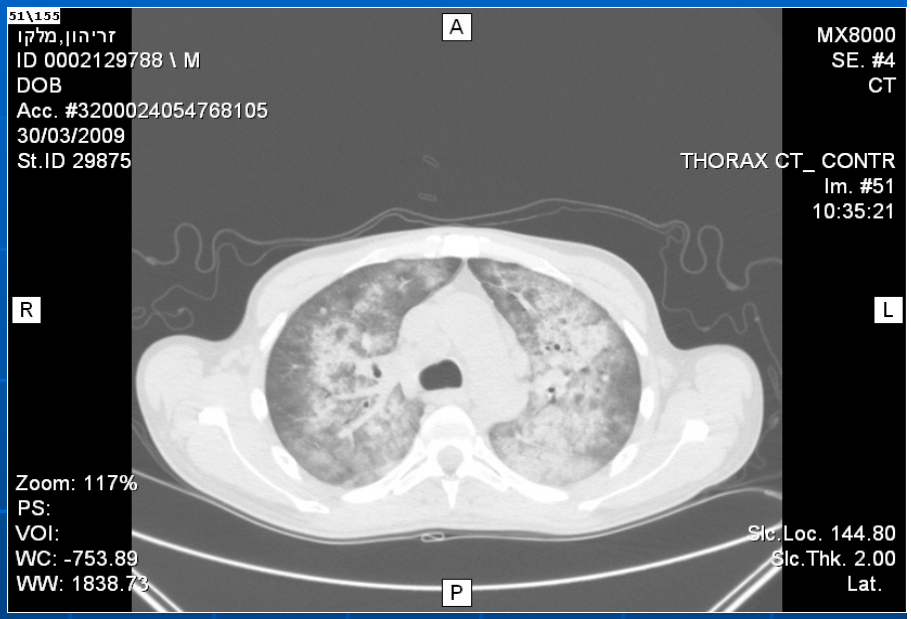
# Case 2

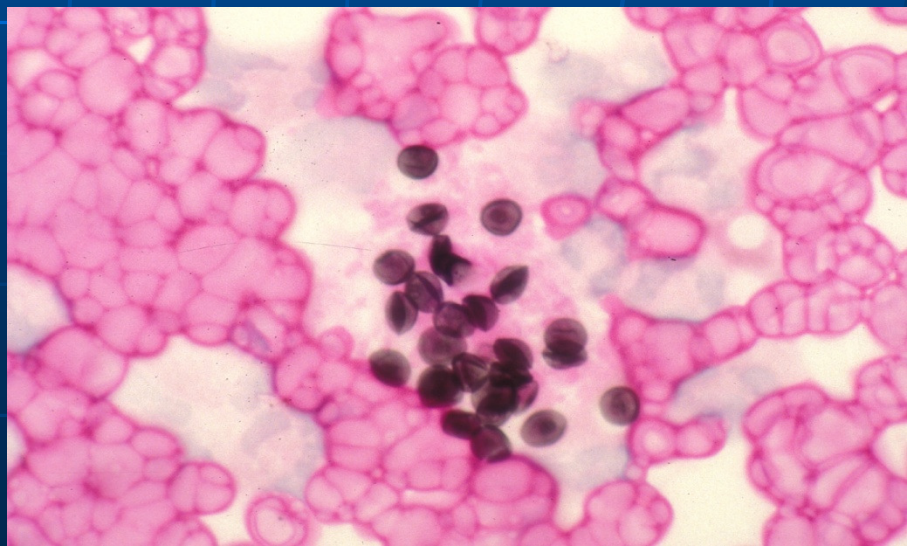
- 33 year old man born in Ethiopia
- One year ago, hospitalized because of increased dyspnea and hypoxia
- Work up revealed

1. HIV positivity CD4 =200 cells/ µL

1. BAL : PCP pneumonitis
2. Cotrimoxazole (septrin) 21 days and prednisone
1. improvement

- Non compliance -no follow up



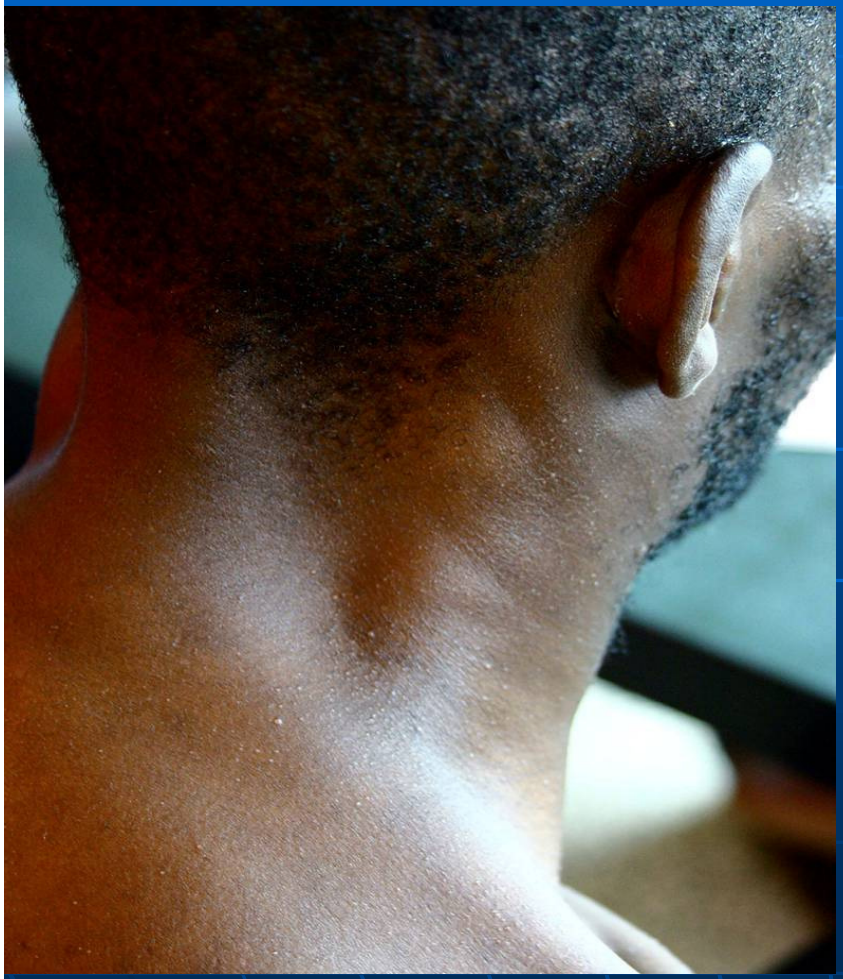



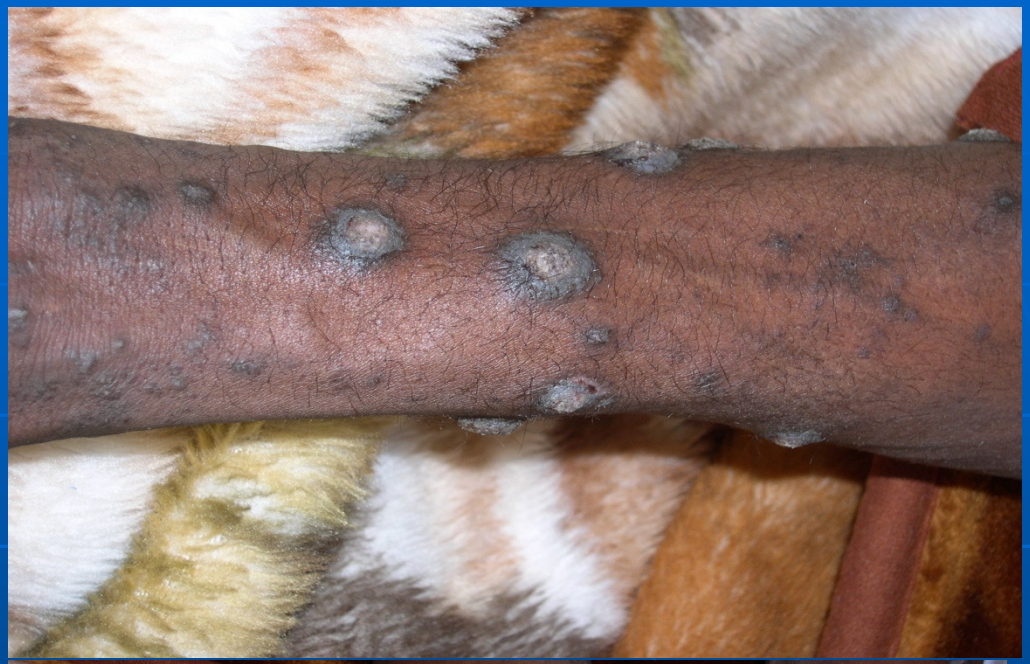
# Case 2

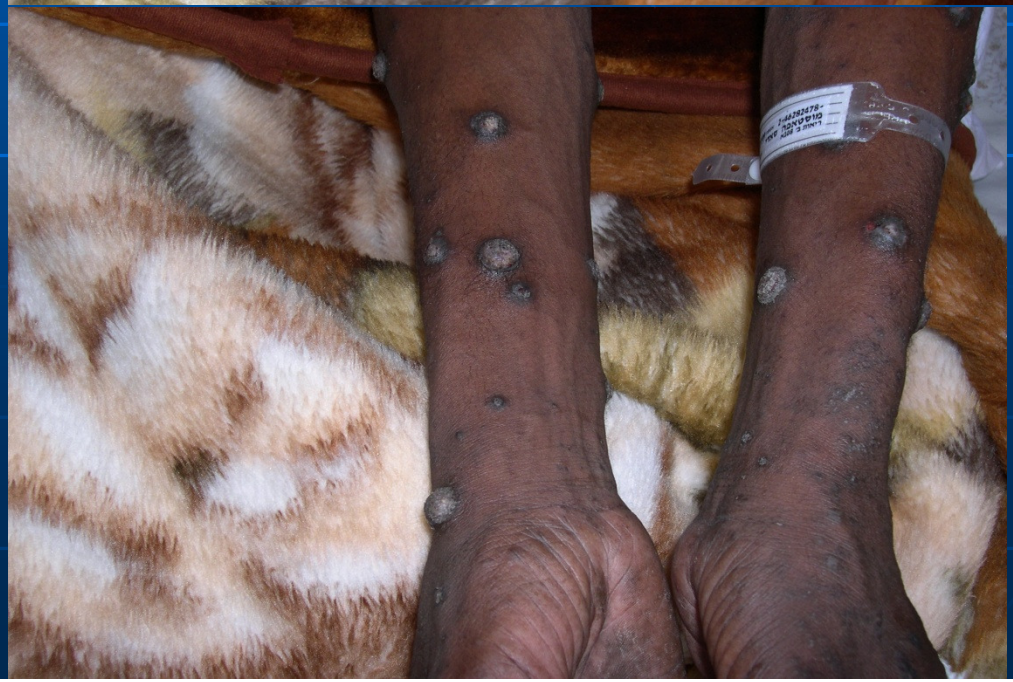
- Few months later, he complained :
  *cough, dry sputum*
  *dizziness worsening headache,*
  *deviation of the walk on the left side*
  *No confusion, no fever*

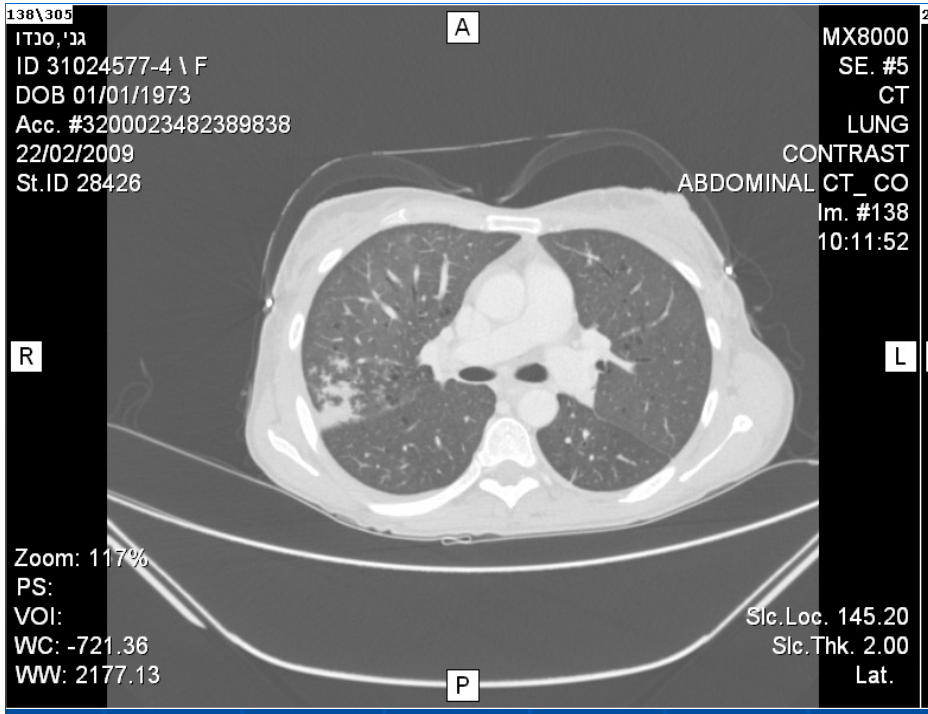
- *Physical examination:*
  *Looks very sick, cachexia*
  Cervical lymph nodes
  Bilat firm pruritic nodules on the arms and legs

- Laboratory examination :
  CD4 : 26 cells / µL
  Sputum negative for AFB in ZN stain





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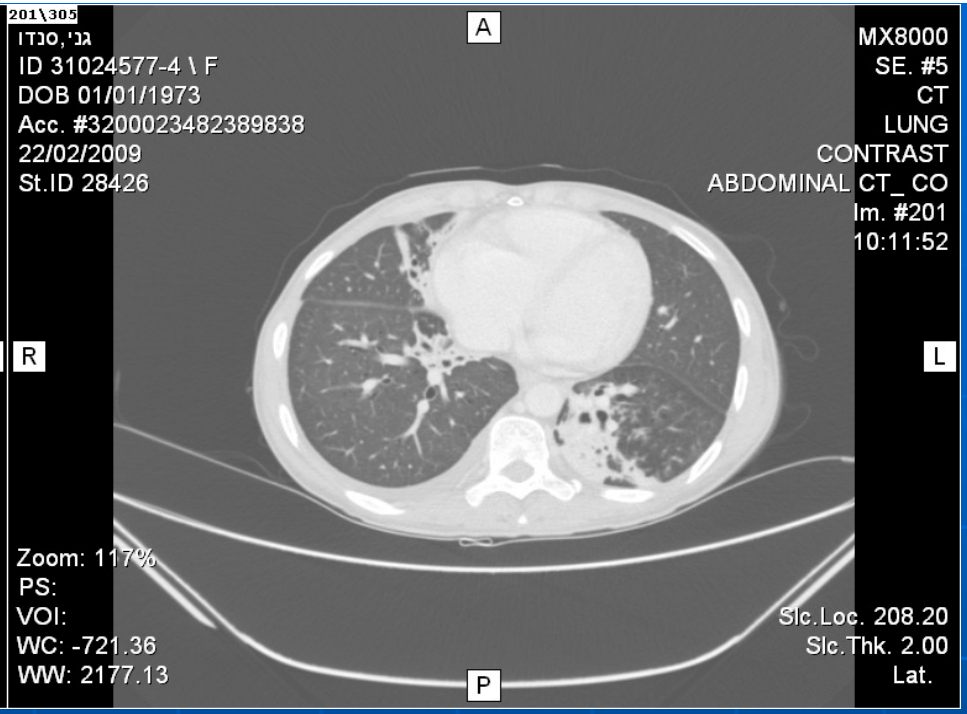
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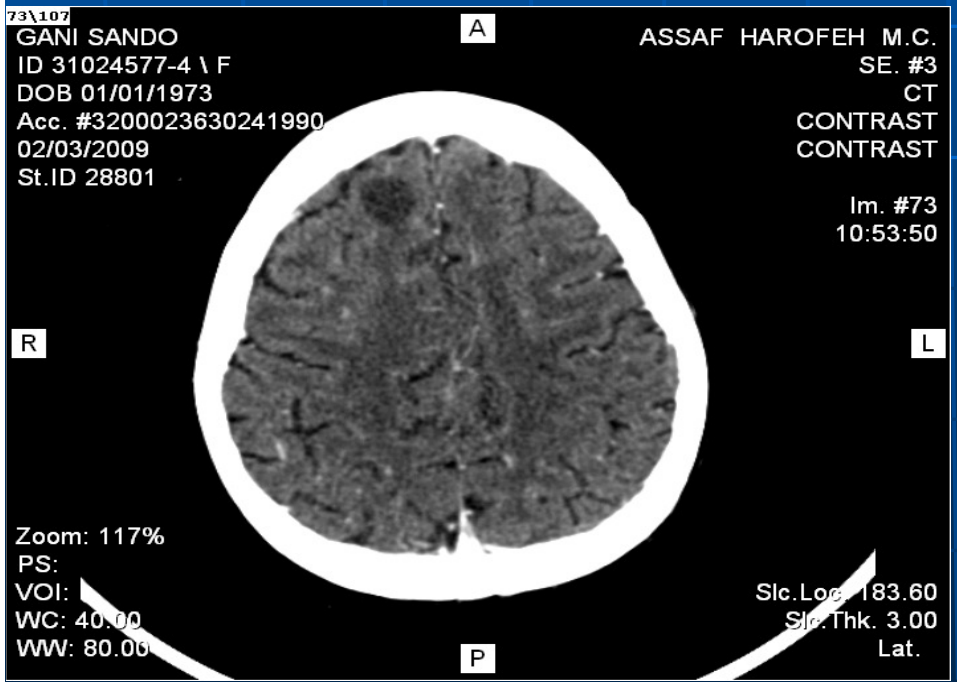
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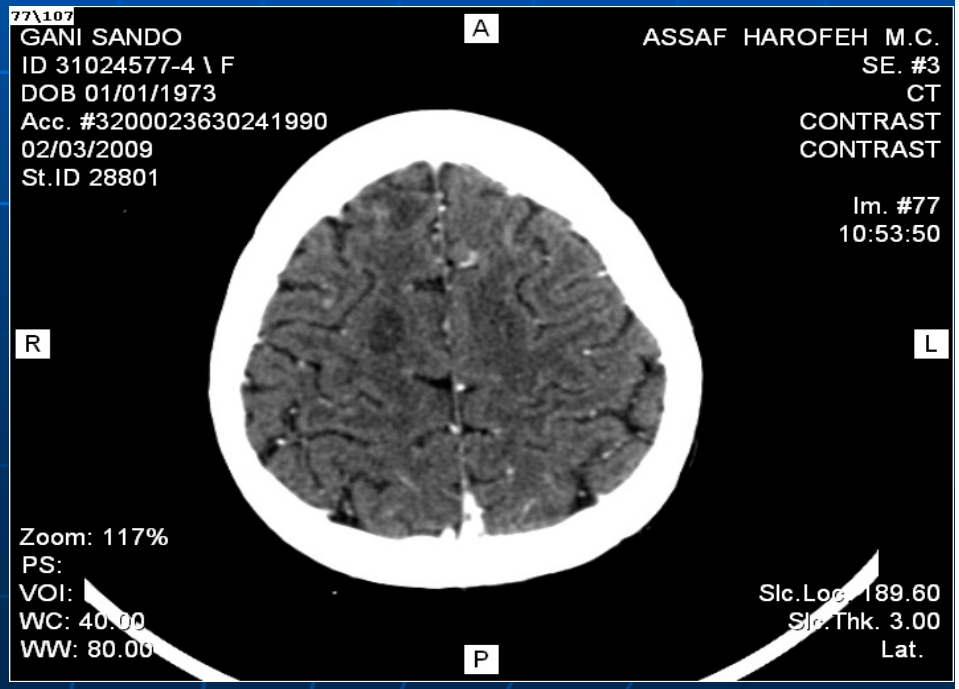
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# Case Report (2)

- Cerebro Spinal Fluid: clear colorless
  normal opening pressure, protein normal
  glucose : 100 mg - no pleocytosis

- Differential Diagnosis:

1. Infectious (*Cryptococcal toxoplasomosis, CMV, Nocardia, MTB)*
1. Malignancy – Lymphoma

- Skin biopsy: prurigo nodularis (*epidermal proliferation*)

- LN biopsy: caseiting granuloma

*Anti TB treatment ( INH, RF, ETB, PZA) and HAART (EFV regimen)*

# Extra Pulmonary TB

- Very frequent in HIV infected people (50% /15%)
- Related to the degree of immunosuppression (>70% when CD4< 200)
- Children : high frequency of meningitis and progressive disease

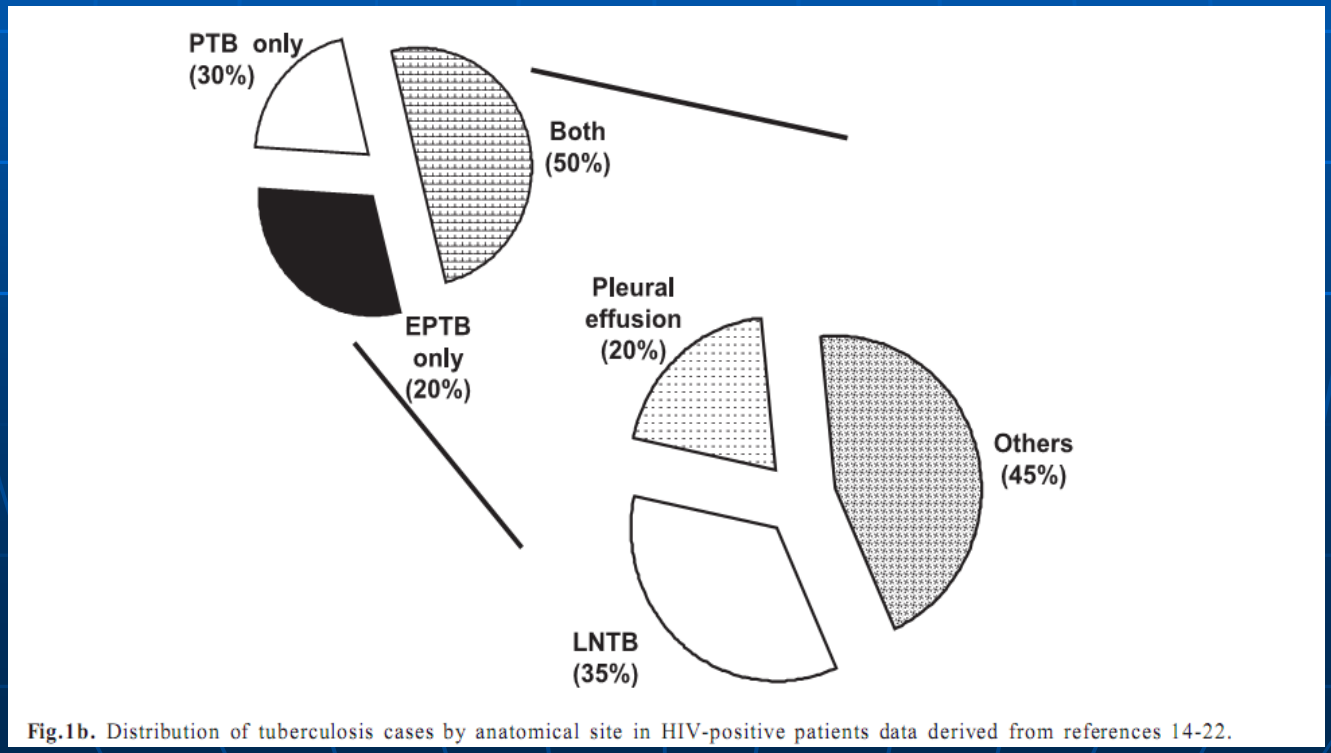
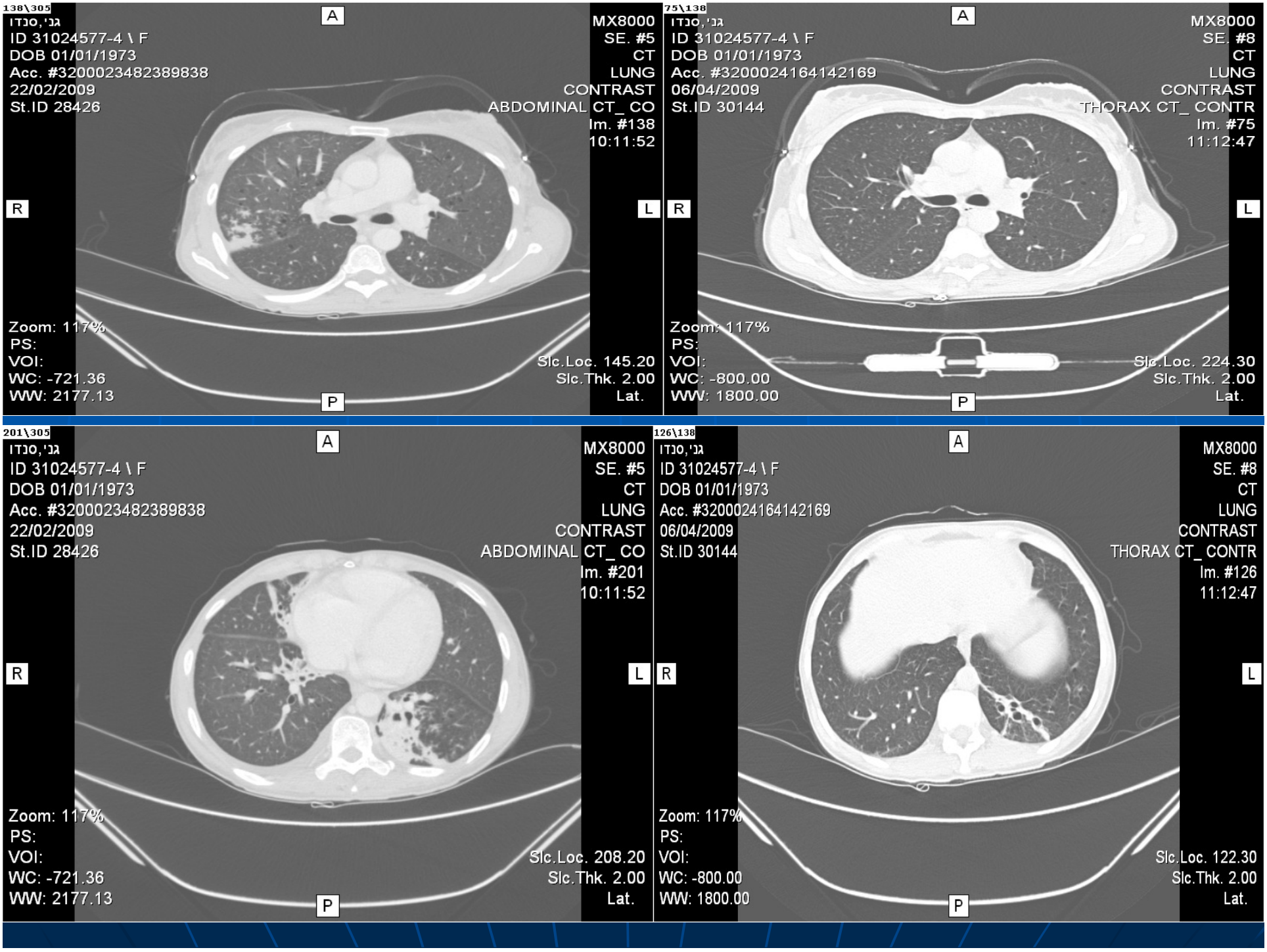



**Fig.1b.** Distribution of tuberculosis cases by anatomical site in HIV-positive patients data derived from references 14-22.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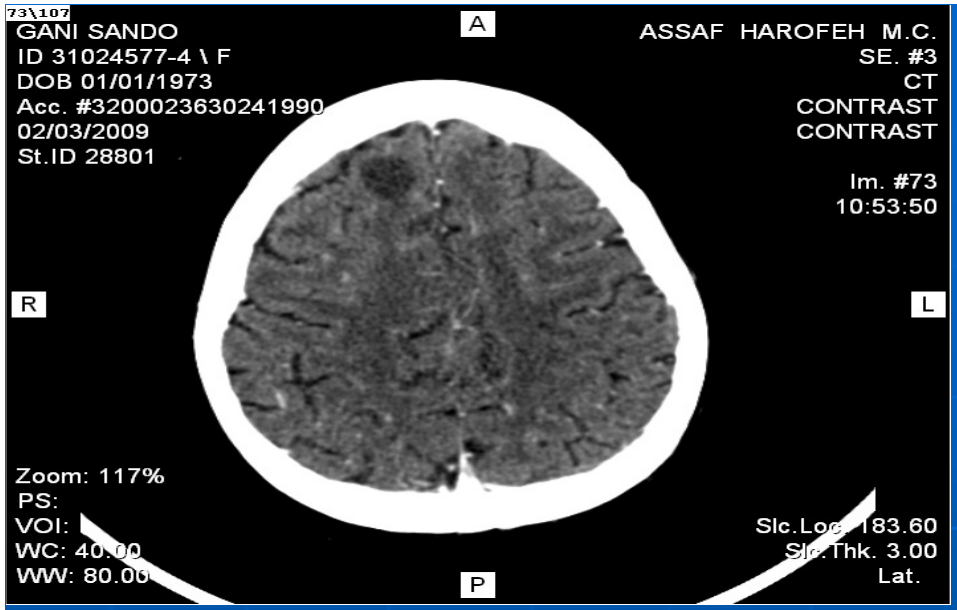
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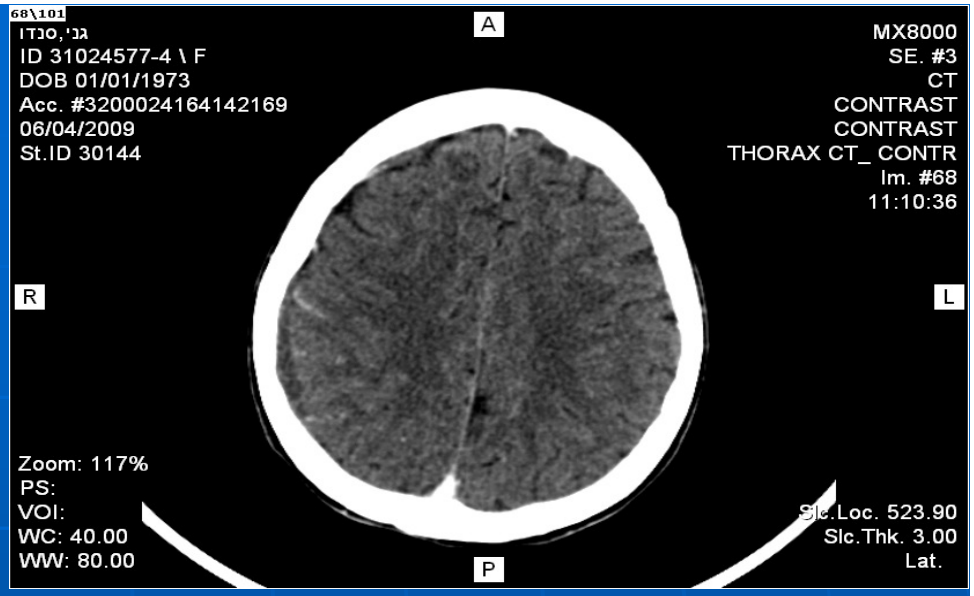
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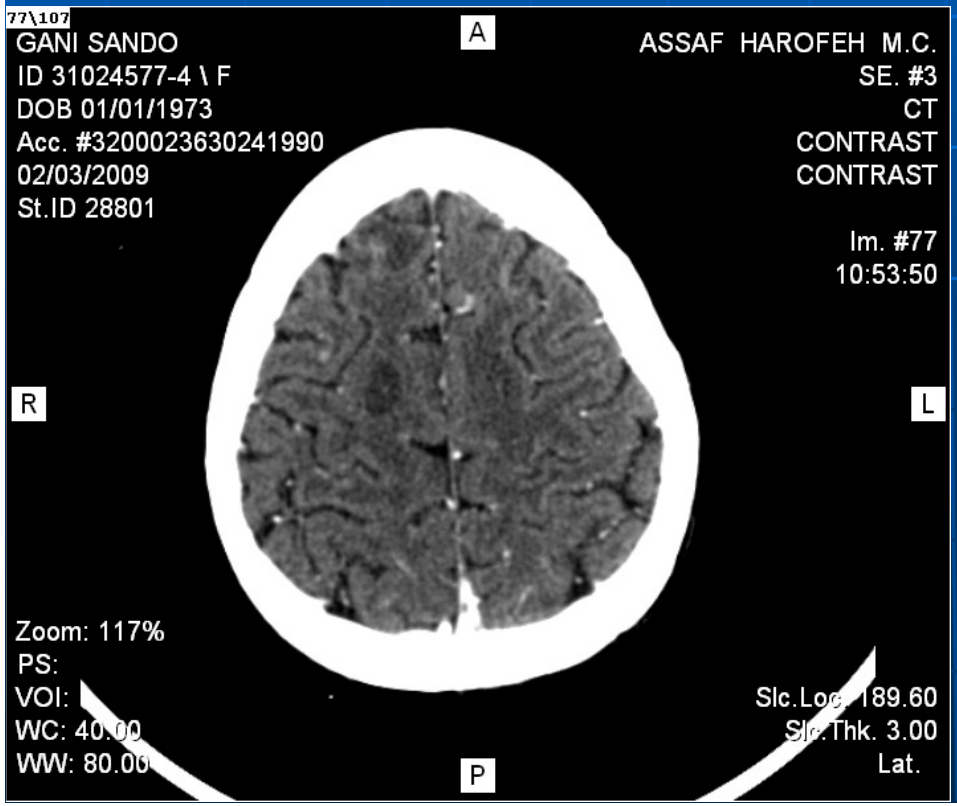
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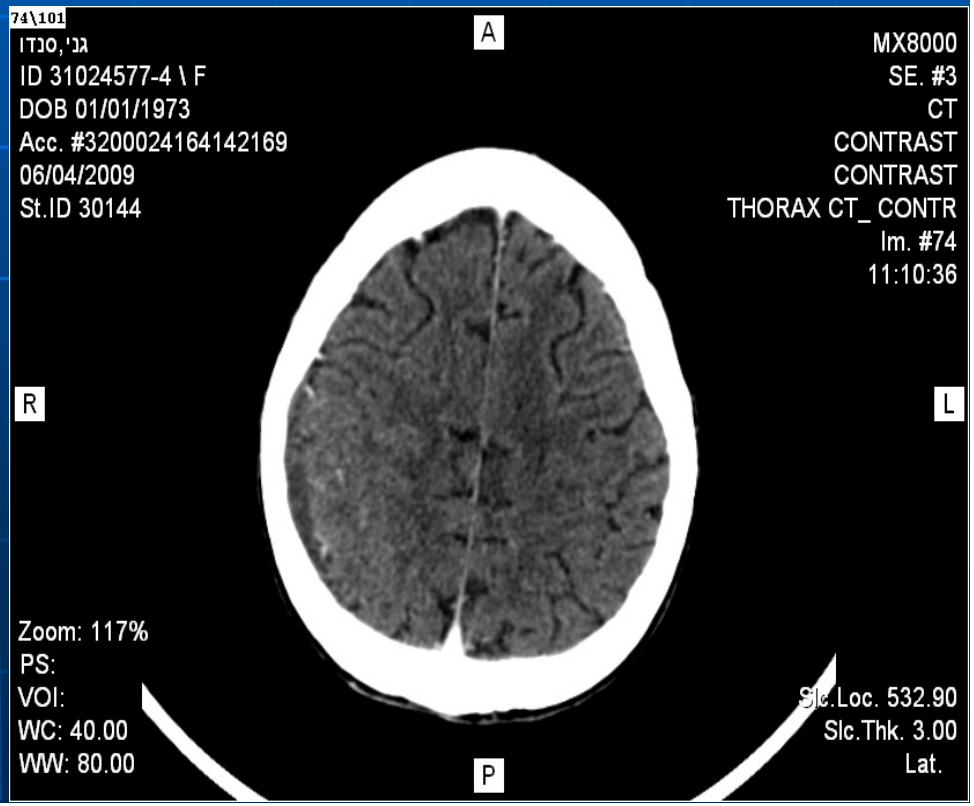
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# Key points 1

- Tuberculosis  is the major cause of morbidity and mortality in HIV infected
- HIV increased the rate of progression  and reactivation of TB
- HIV modifies the presentation of TB and make diagnosis difficult with a high frequency of EPTB
- TB accelerates the progression of HIV (TNF )

***All HIV infected should be evaluated for TB***

***All TB infected should be offered HIV test***

# Key points 2

- Treat TB before over initiating HAART
- Rifampicin has significant drug interaction with ARV drugs
- Understand paradoxical reaction
- Identify drug resistance
- High suspicion, early institution of anti TB drugs and close monitoring is the key to successful management

Thank you !!!!

# Child / Adult TB/HIV

- Tuberculosis infection

  children — recent transmission

  adult — reactivation

- Incidence :

  Children vs adults — Low incidence in well controlled TB country

  20 fold increase TB incidence in HIV + / HIV –

- High rate of mortality and morbidity

- Disease severity: age (<3 years) life threatening manifestations

  immune status

- Diagnosis: close contact+ TST+ Xray (IGRA)