

Symposium: Bridges between nephrology and infectious diseases:

Interactive round

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Case

- 47- year old man

Medical history:

- 1999: familial dilated cardiomyopathy (DCM)
- 2007 : heart transplantation
- Renal failure due to cyclosporine toxicity
- 09/2009: hemodialysis
- 10/2012: kidney transplantation



Case

11/2012 admission with fever and general weakness

Clinical Presentation:

- HR: 100/min BP: 130/80 mmHg T°: 38.4°C
- Normal clinical examination

Medication:

Corticosteroids

Mycophenolate Mofetil (2g)

Tacrolimus (FK levels 12-15)

Case

Laboratory test:

C-reactive proteine	25,3 mg/L	(<5,0)
Creatinine	1,28 mg/dl	(0,67-1,17)
WBC count	7,1 10**9/L	(4,0-10,0)

Urineculture: E. Coli
CMV PCR negative

Radiology:

Chest X-ray -
Ultrasound abdomen -

R/ Broad spectrum antibiotics (Augmentin IV - 10 days)

Good clinical evolution

Case

12/2012 Re-admission with fever and general weakness

Laboratory test:

C-reactive protein	63,0 mg/L	(<5,0)
Creatinine	1,43 mg/dl	(0,67-1,17)
WBC count	8,5 10**9/L	(4,0-10,0)

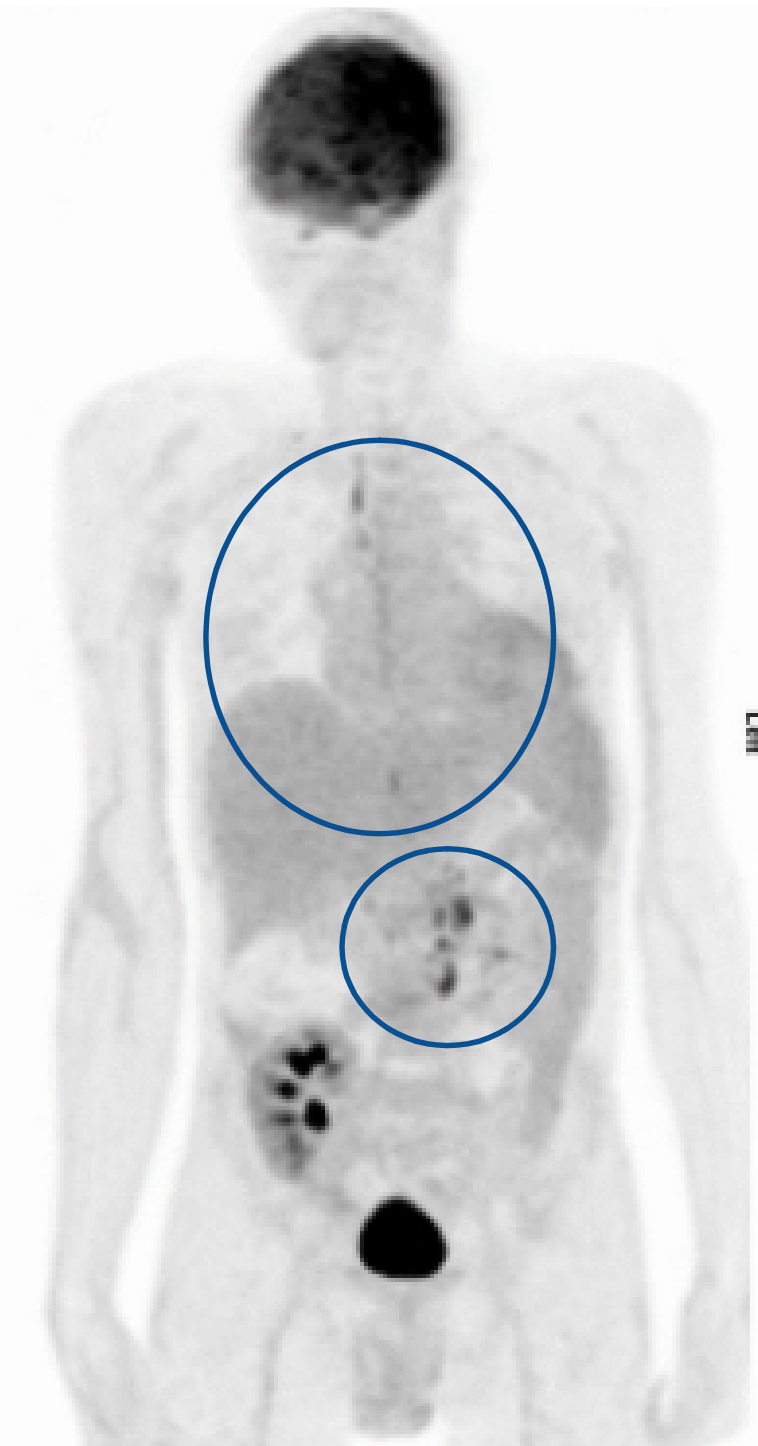
R/ Piperacillin - Tazobactam

Fever after 1 week of therapy



Investigations?

- 1 - WBC, CRP, blood cultures,
urine analysis, CX-ray,
ultrasound abdomen
- 2 - WBC, CRP, urine analysis,
EBV-PCR, CT-scan thorax-abdomen
- 3 - WBC, CRP, blood cultures,
urine analysis, EBV- PCR, PET- CT
- 4 - Wait and see

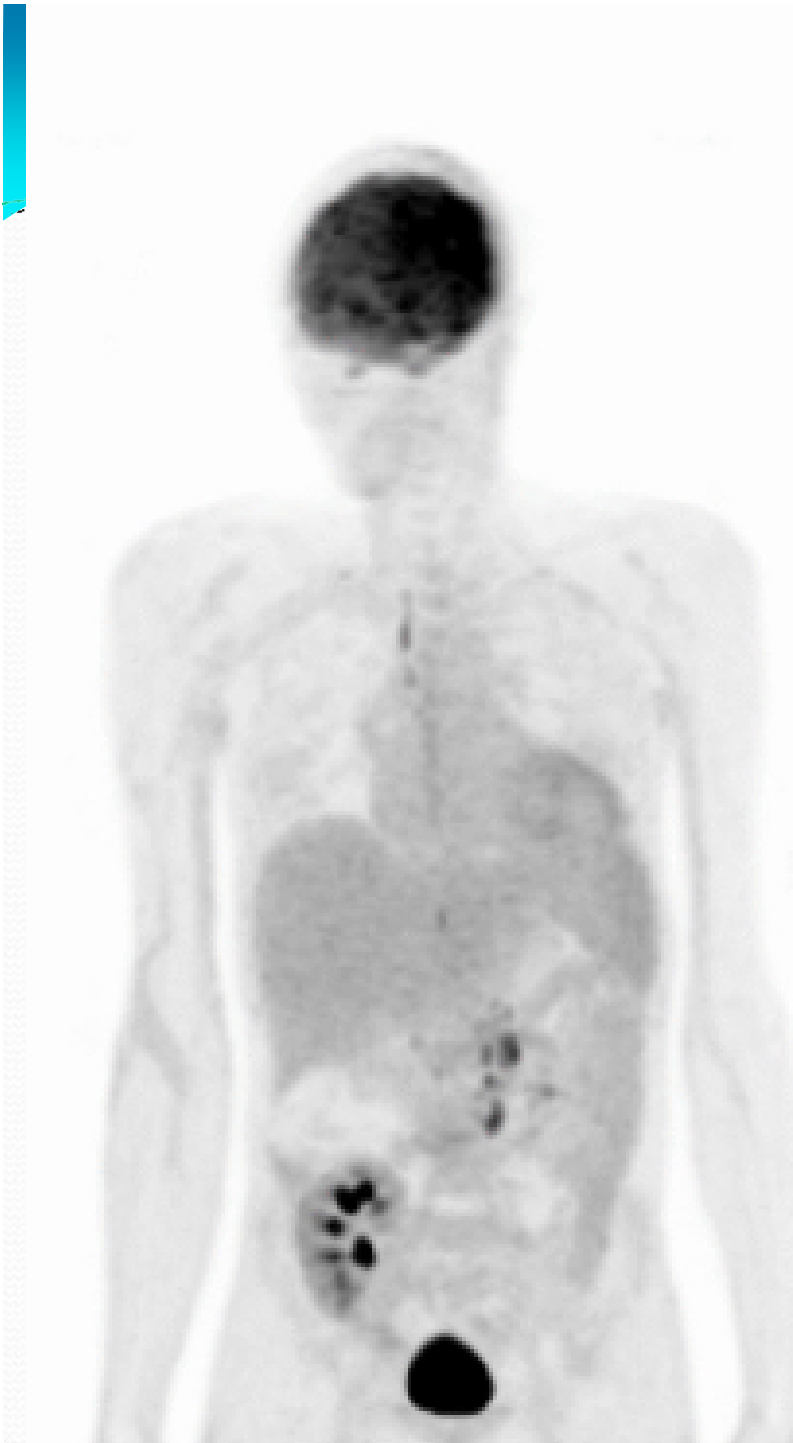


**EBV PCR 4,71 log
copies/mL**



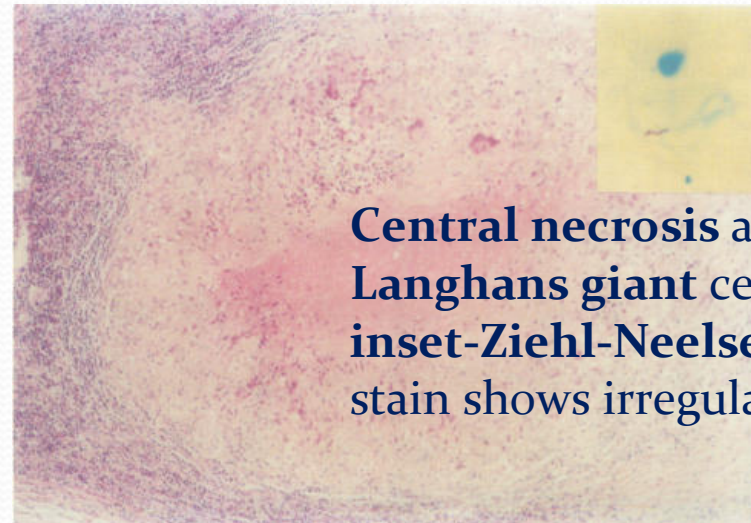
Investigations?

- 1 - Bone-marrow aspiration,
biopsy of a lymph node
- 2 - Biopsy of a lymph node
- 3 - Reduction of
immunosuppression
and new PET after 2 months
- 4 - Wait and see



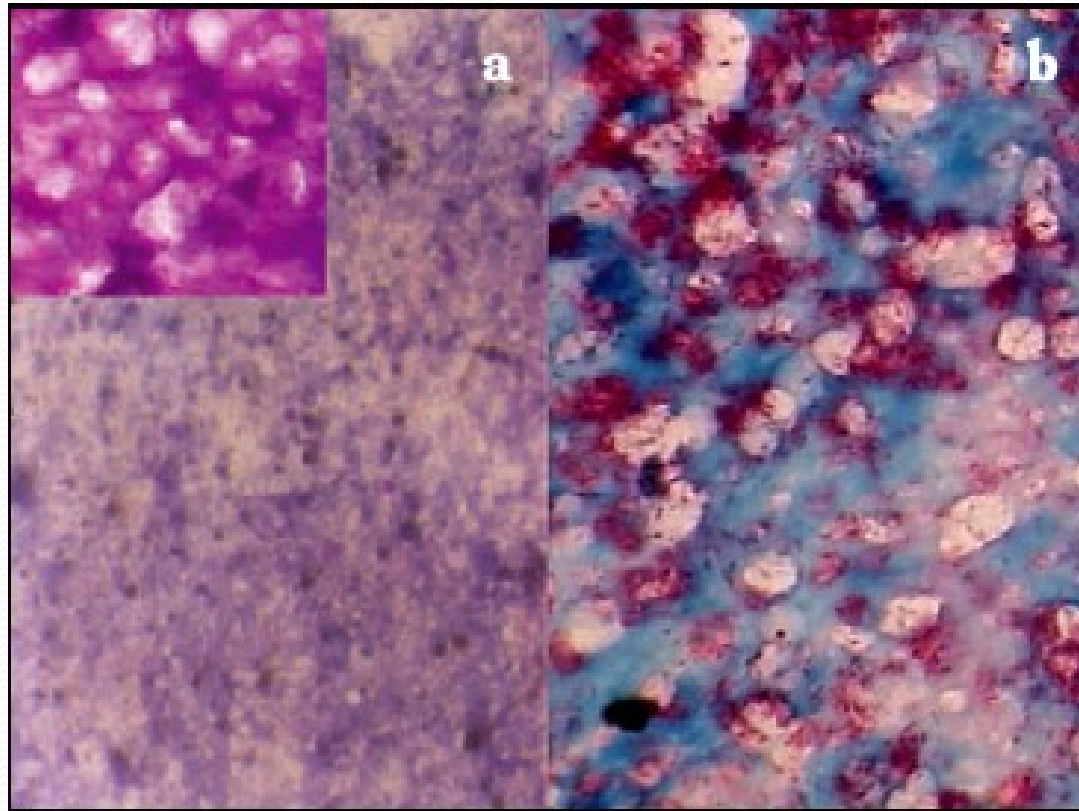
- Bone marrow aspiration
 - Cytology normal
 - Pathology normal-> NO LYMPHOMA

- Biopsy lymph node



**Central necrosis and
Langhans giant cells /
inset-Ziehl-Neelsen
stain shows irregular rods**

- Biopsy lymph node



INTRACELLULAR INCLUSIONS

Figure 1: (a) Cytoaspirate showing scattered foamy macrophages over a necrotic background, MGG, x 400 (inset – foamy macrophages, x1000). (b) ZN staining of the cytoaspirate demonstrating foamy macrophages stacked with acid fast bacilli (x1000).

- Culture

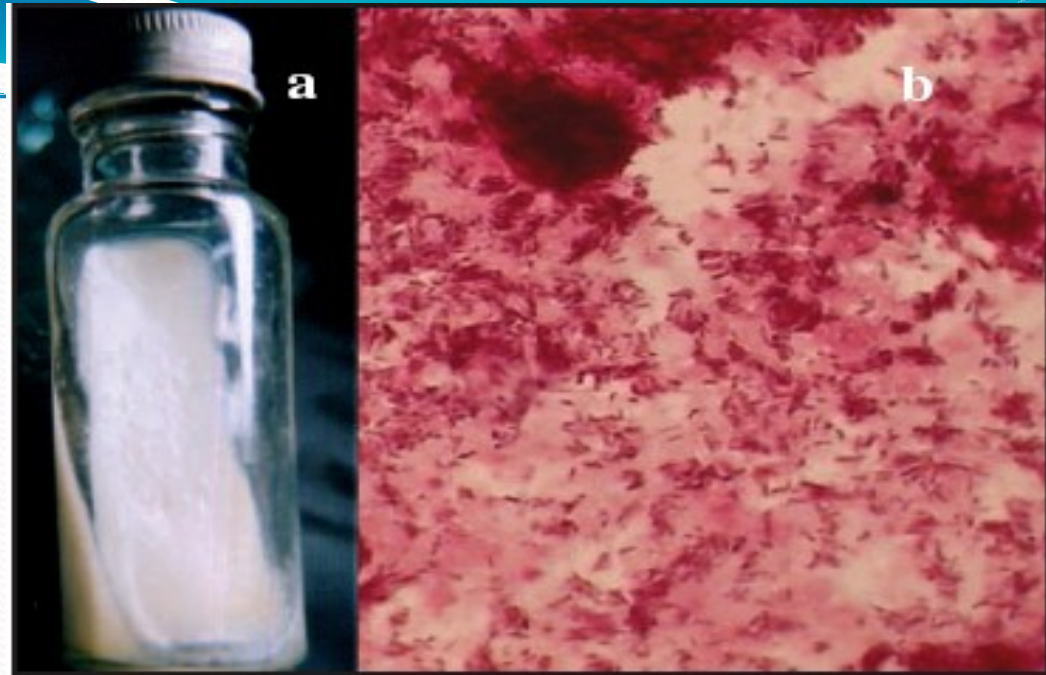


Figure 2: (a) LJ slope showing characteristic smooth discrete dull white colonies of *Mycobacterium avium* complex after 21 days of incubation. (b) ZN staining from the growth of LJ slope demonstrating short curved acid fast bacilli (x1000).

- Growth of visible colonies on **solid media** (eg, Middlebrook 7H11 media and/or Lowenstein-Jensen media) : 2-4 weeks generally at 35 to 37°C.
- Primary cultures in modern **liquid media** (BACTEC 12B broth or Mycobacteria growth indicator tube [MGIT] broth) : 14 days

Next step?

1. This is a **typical** mycobacterial infection, treat with isoniazid , rifampicin , pyrazinamide , and ethambutol
2. This is an **atypical** mycobacterial infection, treat with clarithromycin, ethambutol, rifampicin
3. This is an **atypical** mycobacterial infection, treat with clarithromycin, ethambutol, rifampicin and wait for culture
4. This is an **atypical** mycobacterial infection, treat with clarithromycin, ethambutol, rifampicin and wait for culture and perform PCR



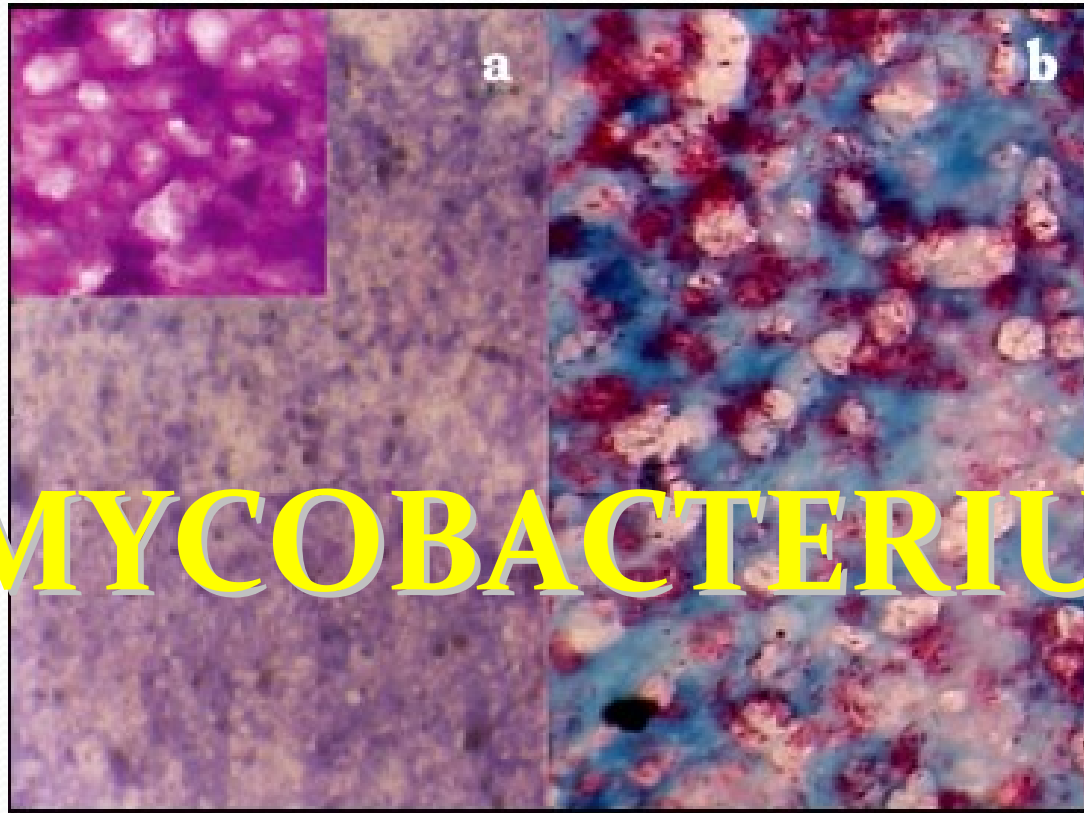
Next step?

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3. This is an **atypical** mycobacterial infection, treat with clarithromycin, ethambutol, rifampicin and wait for culture
4. **This is an atypical mycobacterial infection, treat with clarithromycin, ethambutol, rifampicin and wait for culture and perform PCR**

- Biopsy lymph node



INTRACELLULAR
INCLUSIONS

MYCOBACTERIUM AVIUM

Figure 1: (a) Cytoaspirate showing scattered foamy macrophages over a necrotic background, MGG, x 400 (inset – foamy macrophages, x1000). (b) ZN staining of the cytoaspirate demonstrating foamy macrophages stacked with acid fast bacilli (x1000).



Therapy

- Clarithromycin (1000 mg three times per week) or azithromycin (500 mg three times per week) PLUS
- Rifampicin (600 mg three times per week) or rifabutin (300 mg three times per week) PLUS
- Ethambutol (25 mg/kg three times per week)



Immunosuppression?

1. Stop Cellcept, continue Medrol and low FK through level ($6 \mu\text{g/l}$)
2. Stop Cellcept and stop medrol and higher tacrolimus through level ($8-10 \mu\text{g/l}$)
3. Continue current immunosuppressive therapy

Immunosuppression?

0%

1. Stop Cellcept, continue Medrol and low FK through level ($6 \mu\text{g/l}$)

0%

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01/2013:

Persistent fever and inflammation

C-reactive protein 130 mg/L ($<5,0$)

-> association of isoniazid and pyridoxin

02/2013:

Fever

CT scan: splenomegaly + lymph nodes

03/2013: new lymph node biopsy

- Pathology: mycobacterial infection

- Microbiology:

Auramine culture +

Direct PCR and sequencing

(A) Alignment of ITS fragments used in the real-time PCR assay of various mycobacterial species.

B

<i>M. avium</i> subsp <i>paratuberculosis</i>	1	50
<i>M. avium</i> subsp <i>avium</i> MavD	GGGGTGTGGTGTGTTGAGTATTGGATAGTGGTTGCGAGCATCTAGATGAGC	
<i>M. avium</i> subsp <i>avium</i> MavE	GGGGTGTGGTGTGTTGAGTATTGGATAGTGGTTGCGAGCATCTAGATGAGC	
<i>M. avium</i> subsp <i>avium</i> MavC	GGGGTGTGGTGTGTTGAGTATTGGATAGTGGTTGCGAGCATCTAGATGAGC	
<i>M. avium</i> subsp <i>silvaticum</i>	GGGGTGTGGTGTGTTGAGTATTGGATAGTGGTTGCGAGCATCTAGATGAGC	
<i>M. avium</i> subsp <i>avium</i> MavA	GGGGTGTGGTGTGTTGAGTATTGGATAGTGGTTGCGAGCATCTAGATGAGC	
<i>M. avium</i> subsp <i>avium</i> MavB	GGGGTGTGGTGTGTTGAGTATTGGATAGTGGTTGCGAGCATCTAGATGAGC	
primerF/genusprobe	GGGGTGTGGTGTGTTGAG TGGATAGTGGTTGCGAGCATC	
<i>M. avium</i> subsp <i>paratuberculosis</i>	51	100
<i>M. avium</i> subsp <i>avium</i> MavD	GCATGGTCTCCGTGGCCGGCGTTCATCGAAATGTGTAATTTCTTTT.A	
<i>M. avium</i> subsp <i>avium</i> MavE	GCATGGTCTTCGTGGCCGGCGTTCATCGAAATGTGTAATTTCTTTT.A	
<i>M. avium</i> subsp <i>avium</i> MavC	GCATGGTCTTATGGCCGGCGTTCATCGAAATGTGTAATTTCTTTT.A	
<i>M. avium</i> subsp <i>silvaticum</i>	GCATGGTCTTCGTGGCCGGCGTTCATCGAAATGTGTAATTTCTTTT.A	
<i>M. avium</i> subsp <i>avium</i> MavA	GCATGGTCTTCGTGGCCGGCGTTCATCGAAATGTGTAATTTCTTTT.A	
<i>M. avium</i> subsp <i>avium</i> MavB	GCATGGTCTTCGTGGCCGGCGTTCATCGAAATGTGTAATTTCTTTT.A	
aviumprobe	GGCCGGCGTTCATCGAAAT	
<i>M. avium</i> subsp <i>paratuberculosis</i>	101	150
<i>M. avium</i> subsp <i>avium</i> MavD	ACTCTTGTGTGTAAGTAAGTGTGTTAAGGGCGCATGGTGGATGCCTTGGCA	
<i>M. avium</i> subsp <i>avium</i> MavE	ACTCTTGTGTGTAAGTAAGTGTGTTAAGGGCGCATGGTGGATGCCTTGGCA	
<i>M. avium</i> subsp <i>avium</i> MavC	ACTCTTGTGTGTAAGTAAGTGTGTTAAGGGCGCATGGTGGATGCCTTGGCA	
<i>M. avium</i> subsp <i>silvaticum</i>	ACTCTTGTGTGTAAGTAAGTGTGTTAAGGGCGCATGGTGGATGCCTTGGCA	
<i>M. avium</i> subsp <i>avium</i> MavA	ACTCTTGTGTGTAAGTAAGTGTGTTAAGGGCGCATGGTGGATGCCTTGGCA	
<i>M. avium</i> subsp <i>avium</i> MavB	ACTCTTGTGTGTAAGTAAGTGTGTTAAGGGCGCATGGTGGATGCCTTGGCA	
<i>M. avium</i> subsp <i>paratuberculosis</i>	151	176
<i>M. avium</i> subsp <i>avium</i> MavD	TCGAGAGCCGATGAAGGACGTGGGAG	
<i>M. avium</i> subsp <i>avium</i> MavE	TCGAGAGCCGATGAAGGACGTGGGAG	
<i>M. avium</i> subsp <i>avium</i> MavC	TCGAGAGCCGATGAAGGACGTGGGAG	
<i>M. avium</i> subsp <i>silvaticum</i>	TCGAGAGCCGATGAAGGACGTGGGAG	
<i>M. avium</i> subsp <i>avium</i> MavA	TCGAGAGCCGATGAAGGACGTGGGAG	
<i>M. avium</i> subsp <i>avium</i> MavB	TCGAGAGCCGATGAAGGACGTGGGAG	
PrimerR	GATGAAGGACGTGGGAG	

Bruijnesteijn van Coppenraet E S et al. J. Clin. Microbiol.
2004;42:2644-2650

Journal of Clinical Microbiology

Direct PCR and sequencing

Mycobacterium genus PCR +
M. Tuberculosis complex PCR -

PCR:

MYCOBACTERIUM GENAVENSE

Therapy:

Pyridoxine 250 mg 1x per week

Ethambutol 800 mg/d

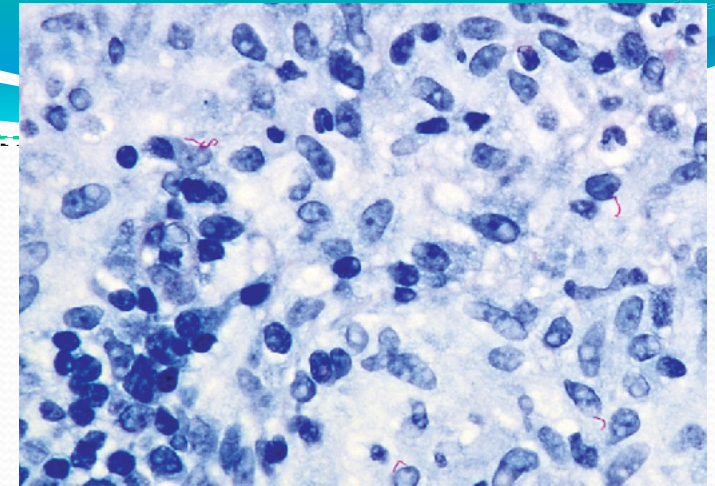
Amikacine 500 mg every 2 days

Moxifloxacin 400 mg/d

Azitromycin 500 mg/d

MYCOBACTERIA

"acid-fastness"



Mycobacterium TUBERCULOSIS

- M. Tuberculosis, M. Bovis, M. Africanum, M. Microti, M. canetti

Mycobacterium LEPRAE

NONTUBERCULOUS mycobacterium (NTM)

- Slowly growing NTM
- Rapidly growing NTM

NONTUBERCULOUS mycobacteria

- Slowly growing NTM (*M. avium* complex, *M. Genavense*,..)
- Rapidly growing NTM (*M. fortuitum* complex, *M. chelonae*, ...)

- Immunocompromised hosts (AIDS pts - solid organ transplant)
- Tap water, pets and gastro-intestinal tract healthy humans
- Slowly growing
- 12,8% *M. Genavense* in AIDS patients
- 5 cases of disseminated infections described in solid organ transplant patients
- Treatment? 2 antimicrobial drugs for a prolonged period + reduction immunosuppressive drugs

Evolution

- Good evolution on PET CT scan
- Good evolution of inflammation
- Try to stop therapy 05/2014 after new PET - CT evaluation

Therapy:

Pyridoxine 250 mg 1x per week
Ethambutol 800 mg/d
Amikacine 500 mg every 2 days
Moxifloxacin 400 mg/d
Azitromycin 500 mg/d





Take home messages

- ❑ transplant patients are highly susceptible to infectious causes of uncommon pathogens
- ❑ diagnosis = challenging because of :
 - absence of specific clinical symptoms
 - difficulties to culture the organism using standard mycobacterial culture procedures
- ❑ molecular techniques

Thank you for your attention !!

